# NEW SUBSTITUTED CYCLIC COMPOUNDS

**Title of the invention :**

New substituted cyclic compounds.

**Field of the invention :**

The present invention relates to new substituted cyclic compounds having very valuable pharmacological characteristics in respect of melatoninergic receptors.

**Description of the prior art :**

The prior art discloses thio-substituted indole amides for use as anti-inflammatory agents (EP 624575, EP 535923), as antagonists of the release of gonadotrophin (WO 9721703), as 5HT-2B or 2C antagonists (WO 9602537), or as synthesis intermediates (Akad. Nauk Gruz., 1991, 141 (3), pp. 545-8 ; Pept. Chem., 1993, 31, pp. 33-6, J. Pharm. Sci., 1973, 62 (8), pp. 1374-5).

Benzo[*b*]thiophene compounds have also been described as anti-inflammatory agents (US 5350748, US 5068248) or as anti-cancer agents (Heterocycles, 1985, 23 (5), pp. 1173-80).

**Background of the invention :**

In the last ten years, numerous studies have demonstrated the major role played by melatonin (5-methoxy-N-acetyltryptamine) in numerous physiopathological phenomena and also in the control of circadian rhythm. Its half-life is, however, quite short owing to its being rapidly metabolised. It is thus very useful to be able to provide the clinician with melatonin analogues that are metabolically more stable and that have an agonist or antagonist character on the basis of which a therapeutic effect that is superior to that of the hormone itself may be expected.

In addition to their beneficial action on disorders of circadian rhythm (J. Neurosurg. 1985, 63, pp 321-341) and sleep disorders (Psychopharmacology, 1990, 100, pp 222-226), ligands of the melatoninergic system have valuable pharmacological properties in respect of the central nervous system, especially anxiolytic and antipsychotic properties (Neuropharmacology of Pineal Secretions, 1990, 8 (3-4), pp 264-272) and analgesic properties (Pharmacopsychiat., 1987, 20, pp 222-223), and also for the treatment of Parkinson's disease (J. Neurosurg. 1985, 63, pp 321-

341) and Alzheimer's disease (Brain Research, 1990, 528, pp 170-174). Those compounds have also shown activity on certain cancers (Melatonin - Clinical Perspectives, Oxford University Press, 1988, pp 164-165), ovulation (Science 1987, 227, pp 714-720), diabetes (Clinical Endocrinology, 1986, 24, pp 359-364), and in the treatment of obesity (International Journal of Eating Disorders, 1996, 20 (4), pp 443-446).

Those various effects take place *via* the intermediary of specific melatonin receptors. Molecular biology studies have shown the existence of a number of receptor sub-types that can bind the hormone (Trends Pharmacol. Sci., 1995, 16, p 50; WO 97.04094). It has been possible to locate some of those receptors and to characterise them for different species, including mammals. In order to be able to understand the physiological functions of those receptors better, it is very valuable to have specific ligands available. Moreover, by interacting selectively with one or other of those receptors, such compounds can be excellent medicaments for the clinician in the treatment of pathologies associated with the melatoninergic system, some of which have been mentioned above.

In addition to the fact that the compounds of the present invention are new, they exhibit very great affinity for melatonin receptors and/or selectivity for one or other of the melatoninergic receptor sub-types.

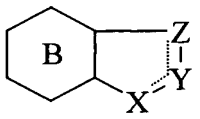
**Detailed description of the invention :**

More specifically, the present invention relates to compounds of formula (I) :

$$R-A-R' \quad (I)$$

wherein :

- ◆ A represents :
  - a ring system of formula (II) :




(II)

wherein • X represents an oxygen, sulphur or nitrogen atom or a group $C(H)_q$ (wherein q is 0, 1 or 2) or $NR_0$ (wherein $R_0$ represents a hydrogen atom, a linear or branched

($C_1$-$C_6$)alkyl group, an aryl group, an aryl-($C_1$-$C_6$)alkyl group in which the alkyl moiety is linear or branched, or $SO_2Ph$),

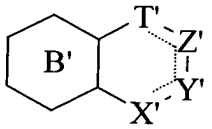
- Y represents a nitrogen atom or a group $C(H)_q$ (wherein q is 0, 1 or 2),
- Z represents a nitrogen atom or a group $C(H)_q$ (wherein q is 0, 1 or 2),

but X, Y and Z cannot represent three hetero atoms simultaneously,

- B represents a benzene or pyridine nucleus,
- the symbol .... means that the bonds may be single or double, it being understood that the valency of the atoms is respected,

wherein R substitutes the ring B and R' substitutes the ring containing the groups X, Y and Z, or R and R' substitute the ring B,

– a ring system of formula (III) :




(III)

wherein
- X' represents an oxygen or sulphur atom or a group $C(H)_q$ (wherein q is 0, 1 or 2),
- Y' represents a group $C(H)_q$ (wherein q is 0, 1 or 2) or $NR_0$ wherein $R_0$ is as defined hereinbefore,
- Z' represents a group $C(H)_q$ (wherein q is 0, 1 or 2) or $NR_0$ wherein $R_0$ is as defined hereinbefore,
- T' represents an oxygen or sulphur atom or a group $C(H)_q$ (wherein q is 0, 1 or 2),

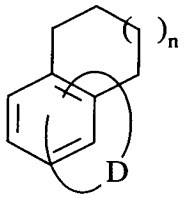
it being understood that, when Y' or Z' represents a hetero atom, the other three variables ((X', Z', T') and (X', Y', T'), respectively) cannot represent a hetero atom,

- the symbol .... is as defined hereinbefore,
- B' represents : * a benzene nucleus,

* a naphthalene nucleus when X', Y', Z' and T' do not simultaneously represent a group $C(H)_q$ (wherein q is 0, 1 or 2),
* or a pyridine nucleus when X' and T' simultaneously represent a group $C(H)_q$ (wherein q is 0, 1 or 2),

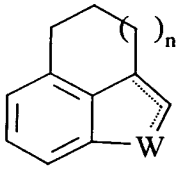
wherein R substitutes the ring B' and R' substitutes the ring containing the groups X', Y', Z' and T', or R and R' substitute the ring B',

– a ring system of formula (IV) :

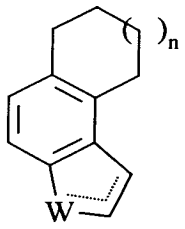


(IV)

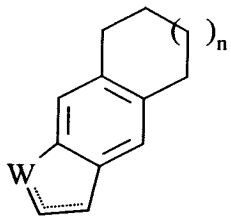
representing the ring systems ($IV_{a-d}$) :



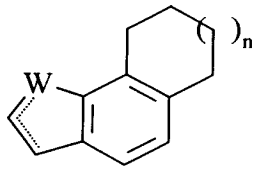
($IV_a$)



($IV_b$)

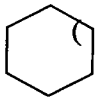


($IV_c$)



($IV_d$)

wherein
- n is an integer such that $0 \leq n \leq 3$,
- W represents an oxygen, sulphur or nitrogen atom, or a group $[C(H)_q]_p$ (wherein q is 0, 1 or 2, and p is 1 or 2) or $NR_0$ wherein $R_0$ is as defined hereinbefore,
- the symbol .... is as defined hereinbefore,

wherein R' substitutes the ring  and R substitutes one or other of the two other rings,

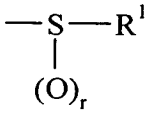
– or a biphenyl group wherein R substitutes one of the benzene rings and R' substitutes the other, or R and R' substitute the same benzene ring,

it being understood that the ring systems of formulae (II), (III) and (IV) and the biphenyl group may be unsubstituted or substituted (in addition to the substituents R and R') by from 1 to 6 radicals, which may be the same or different, selected from $R_a$, $OR_a$, $COR_a$, $COOR_a$, $OCOR_a$, $OSO_2CF_3$, cyano, nitro and halogen atoms,

wherein $R_a$ represents a hydrogen atom, an unsubstituted or substituted linear or branched $(C_1\text{-}C_6)$alkyl group, an unsubstituted or substituted linear or branched $(C_2\text{-}C_6)$alkenyl group, an unsubstituted or substituted linear or branched $(C_2\text{-}C_6)$alkynyl group, a linear or branched $(C_1\text{-}C_6)$polyhaloalkyl group, an unsubstituted or substituted $(C_3\text{-}C_8)$cycloalkyl group, an unsubstituted or substituted $(C_3\text{-}C_8)$cycloalkyl-$(C_1\text{-}C_6)$alkyl group in which the alkyl group is linear or branched, an unsubstituted or substituted $(C_3\text{-}C_8)$cycloalkenyl group, an unsubstituted or substituted $(C_3\text{-}C_8)$cycloalkenyl-$(C_1\text{-}C_6)$alkyl group in which the alkyl group is linear or branched, an aryl group, an aryl-$(C_1\text{-}C_6)$alkyl group in which the alkyl moiety is linear or branched, an aryl-$(C_1\text{-}C_6)$alkenyl group in which the alkenyl moiety is linear or branched, a heteroaryl group, a heteroaryl-$(C_1\text{-}C_6)$alkyl group in which the alkyl moiety is linear or branched, a heteroaryl-$(C_1\text{-}C_6)$alkenyl group in which the alkenyl moiety is linear or branched, an unsubstituted or substituted linear or branched $(C_1\text{-}C_6)$heterocycloalkyl group, an unsubstituted or substituted heterocycloalkenyl group, a substituted or unsubstituted heterocycloalkyl-$(C_1\text{-}C_6)$alkyl group in which the alkyl moiety is linear or branched, or a substituted or unsubstituted heterocycloalkenyl-$(C_1\text{-}C_6)$alkyl group in which the alkyl moiety is linear or branched,

◆ R represents :

– a group of formula (V) :



(V)

wherein • r is an integer such that $0 \leq r \leq 2$,

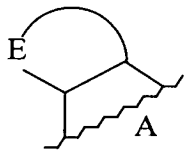
- $R^1$ represents a halogen atom, a group $R_a$, $OR_a$, $COR_a$ or $COOR_a$, wherein $R_a$ is as defined hereinbefore,

it being understood that R cannot represent a group $SO_3H$,

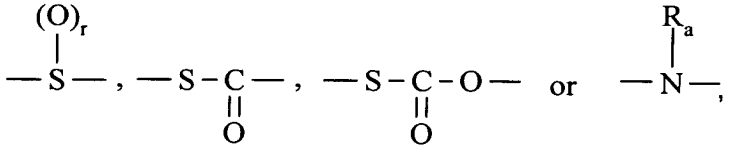
– a group $-NR'_aR''_a$ wherein $R'_a$ and $R''_a$, which may be the same or different, may take any of the values of $R_a$ and also may form, together with the nitrogen atom carrying them, a 5- to 10-membered cyclic group which may contain, in addition to the nitrogen atom, from one to three hetero atoms selected from oxygen, sulphur and nitrogen,

– or, when A represents a ring system of formula (II) or (III) or a biphenyl group, forms, together with two adjacent carbon atoms of the ring structure A carrying it,

a ring of formula (VI) :




(VI)

wherein E represents a group  or ,

wherein r and $R_a$ are as defined hereinbefore,

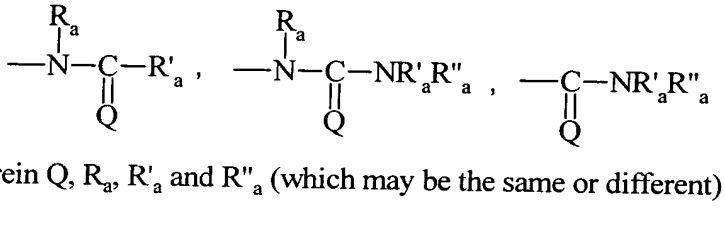
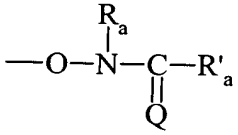
the ring formed containing from 5 to 7 atoms and it being possible for the said ring to contain from 1 to 3 hetero atoms selected from nitrogen, sulphur and oxygen, and one or more unsaturations, and being optionally substituted by one or more radicals, which may be the same or different, selected from $R_a$, $OR_a$, $COR_a$, $COOR_a$, $OCOR_a$, $NR'_aR''_a$, $NR_aCOR'_a$, $CONR'_aR''_a$, cyano, oxo, $SR_a$, $S(O)R_a$, $SO_2R_a$, $CSR_a$, $NR_aCSR'_a$, $CSNR'_aR''_a$, $NR_aCONR'_aR''_a$, $NR_aCSNR'_aR''_a$ and halogen atoms,

wherein $R_a$, $R'_a$ and $R''_a$, which may be the same or different, may take any of the values of $R_a$ and $R'_a$ and $R''_a$ may also form, together with the nitrogen atom carrying them, a cyclic group as defined hereinbefore,

◆ and R' represents a group of formula (VII) :

$$-G-R^2 \qquad (VII)$$

wherein • G represents an alkylene chain $-(CH_2)_t-$ (wherein t is an integer such that $0 \leq t \leq 4$), optionally substituted by one or more radicals, which may be the same or different, selected from $R_a$, $OR_a$, $COOR_a$, $COR_a$ (wherein $R_a$ is as defined hereinbefore) and halogen atoms,

• and $R^2$ represents a group  or  wherein Q, $R_a$, $R'_a$ and $R''_a$ (which may be the same or different) are as defined hereinbefore, it being possible for $R'_a$ and $R''_a$ to form, together with the nitrogen atom carrying them, a cyclic group as defined hereinbefore,

it being understood that :

– "heterocycloalkyl" is taken to mean any saturated mono- or poly-cyclic group containing from 5 to 10 atoms containing from 1 to 3 hetero atoms selected from nitrogen, oxygen and sulphur,

– "heterocycloalkenyl" is taken to mean any non-aromatic mono- or poly-cyclic group containing one or more unsaturations, containing from 5 to 10 atoms and which may contain from 1 to 3 hetero atoms selected from nitrogen, oxygen and sulphur,

– the term "substituted" used in respect of the expressions "alkyl", "alkenyl" and "alkynyl" indicates that the groups in question are substituted by one or more radicals, which may

be the same or different, selected from hydroxy, linear or branched ($C_1$-$C_6$)alkoxy, linear or branched ($C_1$-$C_6$)alkyl, linear or branched ($C_1$-$C_6$)polyhaloalkyl, amino and halogen atoms,

- the term "substituted" used in respect of the expressions "cycloalkyl", "cycloalkylalkyl", "cycloalkenyl", "cycloalkenylalkyl", "heterocycloalkyl", "heterocycloalkenyl", "heterocycloalkylalkyl" and "heterocycloalkenylalkyl" indicates that the cyclic moiety of the groups in question is substituted by one or more radicals, which may be the same or different, selected from hydroxy, linear or branched ($C_1$-$C_6$)alkoxy, linear or branched ($C_1$-$C_6$)alkyl, linear or branched ($C_1$-$C_6$)polyhaloalkyl, amino and halogen atoms,

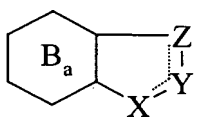
- "aryl" is taken to mean any aromatic, mono- or poly-cyclic group containing from 6 to 22 carbon atoms, and also the biphenyl group,

- "heteroaryl" is taken to mean any aromatic mono- or poly-cyclic group containing from 5 to 10 atoms containing from 1 to 3 hetero atoms selected from nitrogen, oxygen and sulphur,

it being possible for the "aryl" and "heteroaryl" groups to be substituted by one or more radicals, which may be the same or different, selected from hydroxy, linear or branched ($C_1$-$C_6$)alkoxy, linear or branched ($C_1$-$C_6$)alkyl, linear or branched ($C_1$-$C_6$)polyhaloalkyl, cyano, nitro, amino and halogen atoms,

it being understood that :

- when A represents a ring system of formula (IIa) :




(IIa)

wherein X, Y, Z and the symbol ..... are as defined hereinbefore, $B_a$ represents a benzene nucleus and R represents a group of formula (V), then R' cannot represent a group G-$R^2$

wherein G represents a single bond (t=0) and $R^2$ represents a group $-CONR'_aR''_a$ wherein $R'_a$ and $R''_a$ are as defined hereinbefore,

- when A represents a naphthalene nucleus and R represents a group of formula (V), then R' cannot represent a group G-$R^2$ wherein G represents a single bond (t=0) and $R^2$ represents a group $-NHCOR_b$ wherein $R_b$ represents a group $(C_1-C_4)$alkyl or phenol optionally substituted,

- when A represents 1-naphthol and R represents a group of formula (V), then R' cannot represent a group G-$R^2$ wherein G represents a single bond (t=0) and $R^2$ represents a group $-CONHR_c$ wherein $R_c$ represents an optionally substituted phenyl group,

- when A represents a tetrahydronaphthalene nucleus and R represents a group of formula (V), then R' cannot represent a group G-$R^2$ wherein G represents a single bond (t=0) and $R^2$ represents a group $-NR_aCOR_d$ wherein $R_d$ represents a $(C_3-C_8)$cycloalkyl group,

- when A represents an indole nucleus substituted in the 2-position by an optionally substituted phenyl group, then $R^2$ cannot represent a group $-NHCOR_e$ wherein $R_e$ is a group containing an aromatic or non-aromatic mono- or bi-cyclic heterocycle,

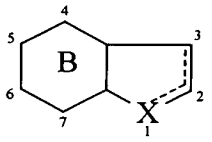
- the compound of formula (I) cannot represent :
  * N-{2-[4-methylthio]-*1H*-3-indolyl]ethyl}formamide
  * 2-(acetylamino)-3-{7-[(2-hydroxyethyl)thio]-*1H*-3-indolyl}propanamide
  * 2-(acetylamino)-3-{2,7-di[(2-hydroxyethyl)thio]-*1H*-3-indolyl}propanamide,

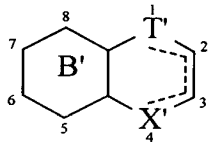
their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

Among the pharmaceutically acceptable acids there may mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid,

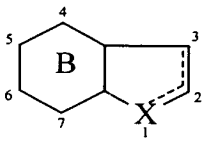
trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, methanesulphonic acid, camphoric acid, oxalic acid etc..

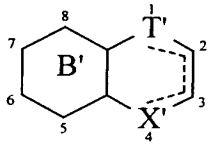
Among the pharmaceutically acceptable bases there may mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, triethylamine, *tert*-butylamine etc..

Preferred compounds of the invention are those wherein A represents a ring system of formula (II) or (III) and, more especially, of formula (II') :  (II') wherein B, X and the symbol .... are as defined hereinbefore,

or of formula (III') :  (III') wherein B', T', X' and the symbol .... are as defined hereinbefore.

The invention advantageously relates to compounds wherein A, which is unsubstituted or substituted by a single substituent (in addition to R and R') preferably in the 2-position (formula II') or in the 3-position (formula III'), represents a ring system of formula (II') :

 (II'), wherein B, X and the symbol .... are as defined hereinbefore, such as, for example, benzothiophene, dihydrobenzothiophene, benzofuran, dihydrobenzofuran, indole, indoline, indan, indene, azaindole, thienopyridine or furopyridine,

or of formula (III') :  (III'), wherein B', T', X' and the symbol .... are as defined hereinbefore, such as, for example, naphthalene, tetrahydronaphthalene, (thio)chroman, (dihydro)benzodioxin, (dihydro)benzoxathiin, (dihydro)benzochromene.

Even more advantageously, the invention relates to compounds wherein A of formula (II') or (III') is substituted by R in the 5-position (formula II') or 7-position (formula III') and by R' in the 3-position (formula II') or 1- or 2-position (formula III').

Preferred substituents R of the invention are those represented by a group of formula (V), (VI) or $-NR'_aR''_a$ (wherein $R'_a$ and $R''_a$ are as defined hereinbefore).

More advantageously, preferred substituents R of the invention are those represented by a group of formula (V) (wherein r is 0 and $R^1$ represents a group $R_a$ as defined hereinbefore), a group $NR'_aR''_a$ (wherein $R'_a$ and $R''_a$ are as defined hereinbefore),
or a group of formula (VI) wherein E represents a group $-S(O)_r-$ or $-N(R_a)-$ wherein r and $R_a$ are as defined hereinbefore.

Even more advantageously, preferred substituents R of the invention are those represented by a group of formula (V) wherein r is 0 and $R^1$ represents an alkyl, polyhaloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl group, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, trifluoromethyl, vinyl, allyl, propargyl, phenyl, naphthyl, benzyl, phenethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, methylcyclopropyl, ethylcyclopropyl, furyl, thienyl, pyridyl, furylmethyl, pyridylmethyl,
or a group $NR'_aR''_a$, wherein $R'_a$ and $R''_a$ (which may be the same or different) represent a hydrogen atom, an alkyl, polyhaloalkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl group, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, trifluoromethyl, vinyl, allyl, propargyl, phenyl, naphthyl, benzyl, phenethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, methylcyclopropyl, ethylcyclopropyl, furyl, thienyl, pyridyl, furylmethyl, pyridylmethyl, or form, together with the nitrogen atom carrying them, a piperazine, piperidine, morpholine or thiomorpholine group.

Preferred substituents R' of the invention are those wherein G represents an unsubstituted or substituted alkylene chain $-(CH_2)_t-$, wherein t is 2 or 3, and $R^2$ represents a group $-N(R_a)-C(=Q)-R'_a$, $-N(R_a)-C(=Q)-NR'_aR''_a$ or $-C(=Q)-NR'_aR''_a$, wherein $R_a$, $R'_a$ and $R''_a$ are as defined hereinbefore.

Even more advantageously, preferred substituents R' of the invention are those wherein G represents a group $-(CH_2)_t-$, wherein t is 2 or 3, and $R^2$ represents a group $-NHC(=O)-R'_a$, wherein $R'_a$ represents an alkyl, polyhaloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloakylalkyl, cycloalkenylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl group, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, trifluoromethyl, vinyl, allyl, propargyl, phenyl, naphthyl, benzyl, phenethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, methylcyclopropyl, ethylcyclopropyl, furyl, thienyl, pyridyl, furylmethyl, pyridylmethyl,

or G represents a group $-(CH_2)_3-$ and $R^2$ represents a group $-C(=O)-NHR_a$, wherein $R_a$ represents an alkyl, polyhaloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloakylalkyl, cycloalkenylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl group, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, trifluoromethyl, vinyl, allyl, propargyl, phenyl, naphthyl, benzyl, phenethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, methylcyclopropyl, ethylcyclopropyl, furyl, thienyl, pyridyl, furylmethyl, pyridylmethyl.

More especially, preferred compounds of the invention are those wherein A represents a ring system of formula (II') or (III') and R represents a group of formula (V), (VI) or $-NR'_aR''_a$.

More advantageously, the invention relates to compounds wherein :

A represents a group of formula (II') or (III') substituted in the 5-position (formula II') or 7-position (formula III') by R and in the 3-position (formula II') or 1- or 2-position (formula III') by R',

and R represents a group $SR_a$, $NR'_aR''_a$ (wherein $R'_a$ and $R''_a$ are as defined hereinbefore) or a group of formula (VI) wherein E represents a group $-S(O)_r-$ or $-NR_a-$ wherein r and $R_a$ are as defined hereinbefore.

Even more advantageously, preferred compounds of the invention are those wherein

A represents a ring system of formula (II') or (III') optionally substituted (in addition to R and R') by a substituent in the 2-position (formula II') or 3-position (formula III'),

substituted in the 5-position (formula II') or 7-position (formula III') by R and in the 3-position (formula II') or 1- or 2-position (formula III') by R',

R represents a group $-SR_a$, $NR'_aR''_a$ (wherein $R_a'$ and $R''_a$ are as defined hereinbefore), or a group of formula (VI) wherein E represents a group $-S(O)_r-$ or $-NR_a-$ wherein r and $R_a$ are as defined hereinbefore,

and R' is such that G represents an unsubstituted or substituted alkylene chain $-(CH_2)_t-$, wherein t is 2 or 3, and $R^2$ represents a group $-N(R_a)-C(=Q)-R'_a$, $-N(R_a)-C(=Q)-NR'_aR''_a$ or $-C(=Q)-NR'_aR''_a$,

wherein $R_a$, $R'_a$ and $R''_a$ are as defined hereinbefore.

Even more especially, the invention relates to (dihydro)benzothiophenes, (dihydro)benzofurans, indoles, indolines, indenes, indans, azaindoles, thieno- or furopyridines optionally substituted in the 2-position, and to dihydronaphthalenes, tetrahydronaphthalenes, naphthalenes or chromans optionally substituted in the 3-position,

substituted in the 5-position (or 7-position, respectively) by a group $-SR_a$ or $-NR'_aR''_a$ wherein $R'_a$ and $R''_a$, which may be the same or different, represent a hydrogen atom, an alkyl, polyhaloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloakylalkyl, cycloalkenylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl group, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, trifluoromethyl, vinyl, allyl, propargyl, phenyl, naphthyl, benzyl, phenethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, methylcyclopropyl, ethylcyclopropyl, furyl, thienyl, pyridyl, furylmethyl,

pyridylmethyl, or $R'_a$ and $R''_a$ form, together with the nitrogen atom carrying them, a piperazine, piperidine, morpholine or thiomorpholine group,

and substituted in the 3-position (or 1- or 2-position, respectively) by a group $-(CH_2)_t-NHCOR'_a$ wherein t is 2 or 3 and $R'_a$ represents an alkyl, polyhaloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloakylalkyl, cycloalkenylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl group, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, trifluoromethyl, vinyl, allyl, propargyl, phenyl, naphthyl, benzyl, phenethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, methylcyclopropyl, ethylcyclopropyl, furyl, thienyl, pyridyl, furylmethyl, pyridylmethyl.

Even more advantageously, preferred compounds of the invention are naphthalenes, optionally substituted in the 3-postion, substituted in the 7-position by a thioalkyl group such as, for example, thiomethyl, thioethyl, thiopropyl, and substituted in the 1-position by a group $-(CH_2)_t-NHCOR'_a$ wherein t is 2 or 3 and $R'_a$ represents an alkyl, polyhaloalkyl or cycloalkyl group, such as, for example, methyl, ethyl, propyl, trifluoromethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

The invention relates very particularly to the compounds of formula (I) that are :

* N-{2-[7-(methylthio)-1-naphthyl]ethyl}acetamide
* N-{2-[7-(methylthio)-1-naphthyl]ethyl}butanamide
* N-{2-[7-(methylthio)-1-naphthyl]ethyl}-1-cyclopropanecarboxamide
* N-{2-[7-(methylthio)-1-naphthyl]ethyl}-2,2,2-trifluoroacetamide
* N-methyl-N'-{2-[7-(methylthio)-1-naphthyl]ethyl}urea
* N-{2-[3-benzoyl-7-(methylthio)-1-naphthyl]ethyl}acetamide
* N-{2-[3-benzyl-7-(methylthio)-1-naphthyl]ethyl}acetamide
* N-{2-[7-(ethylthio)-1-naphthyl]ethyl}acetamide
* N-{2-[7-(propylthio)-1-naphthyl]ethyl}acetamide
* N-[2-(7-mercapto-1-naphthyl)ethyl]benzamide
* N-{2-[7-(allylthio)-1-naphthyl]ethyl}-2-phenylacetamide
* N-{2-[7-(benzylthio)-1-naphthyl]ethyl}heptanamide
* N-methyl-2-[7-(cyclopentylthio)-1-naphthyl]acetamide

* N-cyclohexyl-4-[7-(phenylthio)-1-naphthyl]butanamide
* N-{2-[7-(allylthio)-3-phenyl-1-naphthyl]ethyl}acetamide
* N-{2[7-(benzylthio)-3-phenyl-1-naphthyl]ethyl}acetamide
* N-{2-[5-(2-pyridylthio)benzo[*b*]furan-3-yl]ethyl}acetamide
* N-{[2-benzyl-5-(3-butenylthio)benzo[*b*]thiophen-3-yl]methyl}acetamide
* N-{2-[1-methyl-2-phenyl-5-(propylthio)-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl]ethyl}-acetamide
* N-{2-[5-(allylthio)-2-benzylbenzo[*b*]furan-3-yl]ethyl}-1-cyclopropanecarboxamide
* N-{2-[5-(propylthio)-2-phenylbenzo[*b*]thiophen-3-yl]ethyl}acetamide
* N-{[6-(benzylthio)-2-phenyl-*2H*-3-chromenyl]methyl}acetamide
* N-{2-[5-(isopentylthio)benzo[*b*]thiophen-3-yl]ethyl}acrylamide
* N-{3-[7-(1-propenylthio)-1,2,3,4-tetrahydro-1-naphthyl]propyl}acetamide
* N-{[2-(2-furylmethyl)-5-(2-propynylthio)benzo[*b*]furan-3-yl]methyl}acetamide
* N-[4-(butylthio)-2,3-dihydro-*1H*-2-phenalenyl]propanamide
* ethyl 10-{3-[(cyclohexylcarbonyl)amino]propyl}-1-methyl-*3H*-benzo[*f*]thiochromene-3-carboxylate
* N-[3-(1-oxo-2,3,7,8,9,10-hexahydro-*1H*-benzo[*f*]thiochromen-10-yl)propyl]acetamide
* N-[(2-benzyl-8,9-dihydro-*7H*-thieno[*3,2-f*]thiochromen-1-yl)methyl]acetamide
* N-[2-(*3H*-benzo[*f*]thiochromen-10-yl)ethyl]-2-bromoacetamide
* N-[3-(7-methyl-*7H*-thiochromeno[*6,5-b*]furan-1-yl)propyl]acetamide
* N-methyl-4-(8-hydroxy-7,7-dimethyl-7,8-dihydrothieno[*3',2':3,4*]benzo[*f*]furan-1-yl)-butanamide
* N-{2-[7-amino-3-(cyclopropylmethyl)-1-naphthyl]ethyl}acetamide
* N-{2-[7-(diethylamino)-1-naphthyl]ethyl}-2-phenylacetamide
* N-{2-[7-(hexylamino)-1,2,3,4-tetrahydro-1-naphthyl]ethyl}acetamide
* N-[(6-morpholino-2-phenyl-*2H*-3-chromenyl)methyl]acetamide
* N-[2-(3-benzyl-*3H*-benzo[*e*]indol-9-yl)propyl]-1-cyclohexanecarboxamide
* N-[(2-benzyl-6-ethyl-6,7-dihydrothieno[3,2-f]quinolin-1-yl)methyl]acetamide
* ethyl 9-[2-(phenylacetylamino)ethyl]-1-methyl-*3H*-benzo[*e*]indole-2-carboxylate
* N-[2-(4-methyl-1,2,3,4-tetrahydro[*f*]quinolin-10-yl)ethyl]-2-phenylacetamide

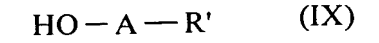
* N-[2-(1-hydroxy-4-methyl-1,2,3,4-tetrahydrobenzo[*f*]quinolin-10-yl)ethyl]-2-phenylacetamide,
* N-{2-[7-(methylsulphinyl)-1-naphthyl]ethyl}acetamide,
* N-{2-[7-(methylsulphonyl)-1-naphthyl]ethyl}acetamide,
* N-{2-[7-(methylthio)-1,2,3,4-tetrahydro-1-naphthyl]ethyl}acetamide,
* N-{2-[7-(methylsulphinyl)-1,2,3,4-tetrahydro-1-naphthyl]ethyl}acetamide,
* N-{2-[7-(methylsulphonyl)-1,2,3,4-tetrahydro-1-naphthyl]ethyl}acetamide,
* N-{2-[7-(benzylthio)-1-naphthyl]ethyl}acetamide,
* N-{2-[7-(benzylsulphinyl)-1-naphthyl]ethyl}acetamide,
* N-{2-[7-(benzylsulphonyl)-1-naphthyl]ethyl}acetamide,
* N-[2-(7-mercapto-1-naphthyl)ethyl]benzamide,
* N-[2-(3-benzyl-7-mercapto-1-naphthyl)ethyl]-1-cyclohexanecarboxamide,
* N-[2-(5-mercaptobenzo[*b*]furan-3-yl)ethyl]acetamide,
* N-[2-(2-benzyl-5-mercaptobenzo[*b*]furan-3-yl)ethyl]-1-cyclopropanecarboxamide.

The enantiomers and diastereoisomers, as well as the addition salts with a pharmaceutically acceptable acid or base, of the preferred compounds of the invention form an integral part of the invention.

The invention relates also to a process for the preparation of compounds of formula (I), which process is characterised in that there is used as starting material the compound of formula (VIII) :

(VIII)

wherein A and R' are as defined hereinbefore, which is subjected to demethylation using conventional agents such as HBr, $AlCl_3$, $AlBr_3$, $BBr_3$ or Lewis acid/nucleophile binary systems such as $AlCl_3/PhCH_2SH$, or $BBr_3/Me_2S$, for example, to obtain the compound of formula (IX) :



(IX)

wherein A and R' are as defined hereinbefore,

– with which, in the presence of trifluoromethanesulphonic acid, there is condensed a thiol of formula (X) :

$$R^1 — SH \qquad (X)$$

wherein $R^1$ is as defined hereinbefore, to obtain the compound of formula (I/a), a particular case of the compounds of formula (I) :

$$R^1 — S — A — R' \qquad (I/a)$$

wherein $R^1$, A and R' are as defined hereinbefore,

which compound of formula (I/a), when $R^1$ represents a group $R_a$ as defined hereinbefore, may be obtained directly starting from the compound of formula (X) by the action of $AlCl_3$ and the thiol of formula (XI) :

$$R_a — SH \qquad (XI)$$

wherein $R_a$ is as defined hereinbefore,

which compound of formula (I/a) may be obtained starting from the compound of formula (I/a'), a particular case of the compounds of formula (I/a) :

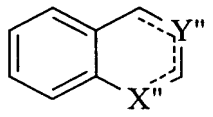
$$HS — A — R' \qquad (I/a')$$

wherein A and R' are as defined hereinbefore, which is reacted in a basic medium with a compound of formula (XII) :

$$R'^1 — M \qquad (XII)$$

wherein $R'^1$ may have any of the meanings of $R^1$ except for hydrogen and M represents a leaving group such as a halogen atom, for example,

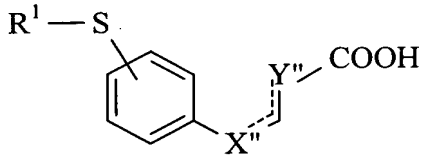
which compound of formula (I/a) may also be obtained, when A represents a ring system of formula (XIII) :



(XIII)

wherein the symbol ..... is as defined hereinbefore, Y" represents a group $C(H)_q$ (wherein q is 0, 1 or 2) or a bond, and X" represents an oxygen, nitrogen or sulphur atom or a group $C(H)_q$ (wherein q is 0, 1 or 2) or $NR_0$ (wherein $R_0$ is as defined hereinbefore), it being understood that when X" represents a nitrogen atom or a group $NR_0$ then Y" represents a bond,

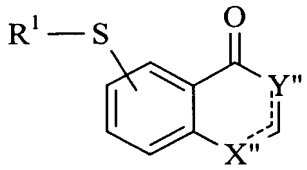
starting from a compound of formula (XIV) :



(XIV)

wherein $R^1$, X", Y" and the symbol ..... are as defined hereinbefore,

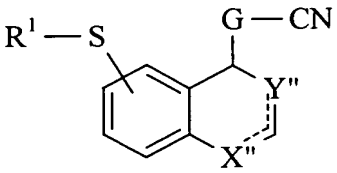
which is cyclised in the presence of polyphosphoric acid to yield the compound of formula (XV) :



(XV)

wherein $R^1$, X", Y" and the symbol ..... are as defined hereinbefore,

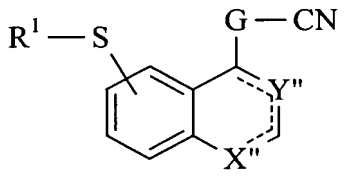
which is subjected to a Wittig reaction and then to reduction to yield the compound of formula (XVI) :



(XVI)

wherein $R^1$, X", Y", G and the symbol ..... are as defined hereinbefore,

which may be oxidised to yield the compound of formula (XVII) :

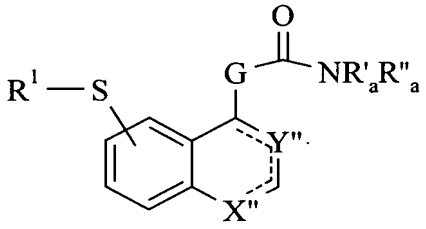


(XVII)

wherein $R^1$, X", Y", G and the symbol ..... are as defined hereinbefore,

which is :

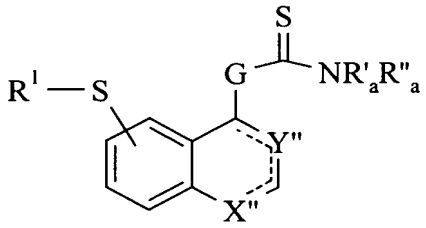
* either hydrolysed in an acid or basic medium and then subjected, after activation to the acid chloride form or in the presence of a coupling agent, to the action of an amine $HNR'_aR"_a$, wherein $R'_a$ and $R"_a$ are as defined hereinbefore, to yield the compound of formula (I/b), a particular case of the compounds of formula (I) :



(I/b)

wherein $R^1$, X", Y", G, $R'_a$, $R"_a$ and the symbol ..... are as defined hereinbefore,

which may be subjected to a thionating agent such as Lawesson's reagent to yield the compound of formula (I/c), a particular case of the compounds of formula (I) :



(I/c)

wherein $R^1$, X", Y", G, $R'_a$, $R"_a$ and the symbol ..... are as defined hereinbefore,

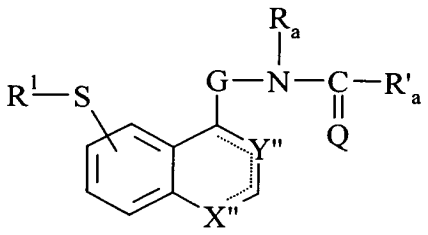
* or reduced and then reacted with :

- an acyl chloride $ClCOR'_a$ or the corresponding anhydride (mixed or symmetrical), wherein $R'_a$ is as defined hereinbefore, optionally followed by the action of a compound of formula (XVIII) :

$$R_{1a} — J \qquad (XVIII)$$

wherein $R_{1a}$ can take any of the meanings of the group $R_a$ except for a hydrogen atom and J represents a leaving group such as a halogen atom or a tosyl group,

and/or by the action of a thionating agent to yield the compound of formula (I/d), a particular case of the compounds of formula (I) :



(I/d)

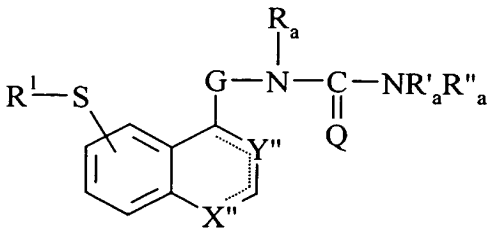
wherein $R^1$, X", Y", G, $R_a$, $R'_a$, Q and the symbol ..... are as defined hereinbefore,

- or with a compound of formula (XIX) :

$$Q=C=N—R'_a \qquad (XIX)$$

wherein Q and $R'_a$ are as defined hereinbefore,

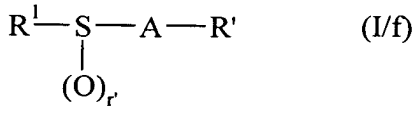
optionally followed by the action of a compound of formula (XVIII) to yield the compound of formula (I/e), a particular case of the compounds of formula (I) :



(I/e)

wherein $R^1$, X", Y", G, $R_a$, $R'_a$, $R"_a$, Q and the symbol .... are as defined hereinbefore,

which compounds (I/a) to (I/e) may be reacted with an oxidising agent such as $H_2O_2$, $NaIO_4$, $KMnO_4$ or NaOCl or meta-chloroperbenzoic acid, for example, to yield the compound of formula (I/f), a particular case of the compounds of formula (I) :



(I/f)

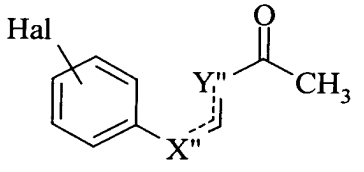
wherein $R^1$, A and R' are as defined hereinbefore and r' represents an integer such that $1 \leq r' \leq 2$,

– or which compound of formula (IX) is converted, by means of the action of reagents such as $POCl_3$, $PCl_5$, $Ph_3PBr_2$, $PhPCl_4$, HBr or HI, into the corresponding halogenated compound of formula (XX) :

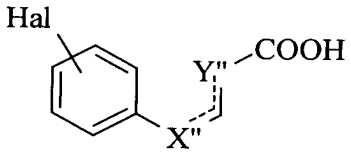


(XX)

wherein A and R' are as defined hereinbefore and Hal represents a halogen atom (which compounds of formula (XX) can be obtained by exchange reactions such as, for example, the treatment of a chlorinated compound with KF in dimethylformamide to yield the corresponding fluorinated compound or the treatment of a brominated compound with KI in the presence of copper salts to yield the corresponding iodinated compound, and which compounds of formula (XX) can also be obtained starting from compounds of formula ($XX_1$) or ($XX_2$) :



($XX_1$)

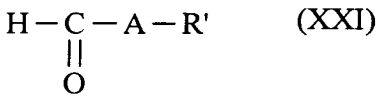


($XX_2$)

wherein Hal, X" and Y" are as defined hereinbefore),

which compound of formula (XX) is :

• either treated with carbon monoxide and $Bu_3SnH$, the reaction being catalysed with palladium(0), to yield the corresponding aldehyde of formula (XXI) :



(XXI)

wherein A and R' are as defined hereinbefore,

which compound of formula (XXI) may alternatively be obtained by customary lithiation methods starting from the halogenated compound of formula (XX), or *via* the corresponding vinyl compound (obtained starting from the compound of formula (XX) by the action of vinyltributyltin and tetrakis palladium) subjected to ozonolysis, or furthermore by direct formylation of the nucleus A, for example according to a Vilsmeier reaction,

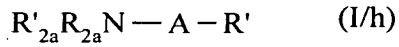
which compound of formula (XXI) is subjected to an oxidising agent to obtain the compound of formula (XXII) :

(XXII)

wherein A and R' are as defined hereinbefore, which is converted, after the action of thionyl chloride and an azide, and then of an acid, into the compound of formula (I/g), a particular case of the compounds of formula (I) :

(I/g)

wherein A and R' are as defined hereinbefore, with which there is condensed one or two molecules of a compound of formula (XVIII) to obtain the compound of formula (I/h), a particular case of the compounds of formula (I) :



(I/h)

wherein A and R' are as defined hereinbefore and $R'_{2a}$ and $R_{2a}$, which may be the same or different, represent a group $R_a$ with the following proviso : $R'_{2a}$ and $R_{2a}$ cannot simultaneously represent a hydrogen atom and cannot form, together with the nitrogen atom carrying them, a cyclic group,

or which compound of formula (XX) is subjected, under conditions of nucleophilic aromatic substitution, to the action of an amine $R'_aR''_aNH$, wherein $R'_a$ and $R''_a$ are as defined hereinbefore ($R'_a$ and $R''_a$ may, *inter alia*, form, together with the nitrogen atom carrying

them, a cyclic group as defined hereinbefore), to yield the compound of formula (I/i), a particular case of the compounds of formula (I) :

$$R'_aR''_aN-A-R' \qquad (I/i)$$

wherein $R'_a$, $R''_a$, A and R' are as defined hereinbefore,

which compounds (I/a) to (I/i) can be purified in accordance with a conventional separation technique, are converted, if desired, into their addition salts with a pharmaceutically acceptable acid or base and, optionally, are separated into their isomers in accordance with a conventional separation technique.

The starting compounds (VIII) are either commercially available or are described in the literature, for example in the Patent Applications EP0447285, EP0527687, EP0562956, EP0591057, EP0662471, EP0745586, EP0709371, EP0745583, EP0721938, EP0745584, EP0737670, EP0737685, or WO9738682.

The invention relates also to a process for the preparation of compounds of formula (I) wherein R represents a ring of formula (VI), which process is characterised in that compounds of formulae (I/a) to (I/i) are used as starting materials, which are cyclised according to methods described in the literature, for example in the Patent Applications EP0708099 or WO9732871.

The compounds of the invention and pharmaceutical compositions comprising them are proving to be useful in the treatment of disorders of the melatoninergic system.

The invention relates also to the compounds of formula ($XX_A$), a particular case of the compounds of formula (XX) :

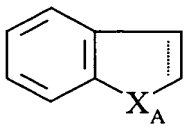
$$Hal-A_A-R'_A \qquad (XX_A)$$

wherein :

- Hal represents a halogen atom (fluorine, chlorine, bromine, iodine),

◆ $A_A$ represents :

– a ring system of formula (a) :

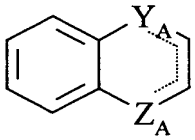


(a)

wherein $X_A$ represents a sulphur atom or a group $C(H)_q$ (wherein q is 0, 1 or 2) or $NR_0$ (wherein $R_0$ is as defined hereinbefore), and the symbol .... is as defined hereinbefore,

wherein the halogen atom substitutes the benzene nucleus and the group $R'_A$ substitutes the 5-membered ring,

– or a ring system of formula (b) :

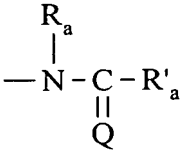
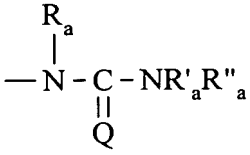


(b)

wherein $Y_A$ and $Z_A$, which may be the same or different, represent an oxygen or sulphur atom or a group $C(H)_q$ (wherein q is 0, 1 or 2), and the symbol .... is as defined hereinbefore,

wherein the halogen atom substitutes the benzene nucleus and the group $R'_A$ substitutes one or other of the two rings,

which ring systems of formula (a) or (b) may be substituted (in addition to the halogen atom and the group $R'_A$) by one or more groups selected from $R_a$, $COR_a$, $COOR_a$, $OCOR_a$ wherein $R_a$ is as defined hereinbefore,

◆ and $R'_A$ represents a group $G\text{-}R^2_A$ wherein G is as defined hereinbefore and $R^2_A$ represents a group  or  wherein $R_a$, $R'_a$, $R''_a$ and Q are as defined hereinbefore,

their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base,
as synthesis intermediates but also as compounds for use in the treatment of disorders associated with the melatoninergic system.

Pharmacological study of the compounds of the invention has in fact shown them to be non-toxic, to have strong affinity for melatonin receptors and to possess important activities in respect of the central nervous system and, in particular, there have been found therapeutic properties in relation to sleep disorders, anxiolytic, antipsychotic and analgesic properties and in relation to the microcirculation, enabling it to be established that the products of the invention are useful in the treatment of stress, sleep disorders, anxiety, seasonal affective disorder, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue resulting from jet lag, schizophrenia, panic attacks, melancholia, appetite disorders, obesity, insomnia, psychotic disorders, epilepsy, diabetes, Parkinson's disease, senile dementia, various disorders associated with normal or pathological ageing, migraine, memory loss, Alzheimer's disease, and also cerebral circulation disorders. In another field of activity, it appears that, in treatment, the products of the invention can be used in sexual dysfunction, that they have ovulation-inhibiting properties and immunomodulating properties and are able to be used in the treatment of cancers.

The compounds will preferably be used in the treatment of seasonal affective disorder, sleep disorders, cardiovascular pathologies, insomnia and fatigue resulting from jet lag, appetite disorders and obesity.

For example, the compounds will be used in the treatment of seasonal affective disorder and sleep disorders.

The present invention relates also to pharmaceutical compositions comprising at least one compound of formula (I), alone or in combination with one or more pharmaceutically acceptable excipients.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral, nasal, per- or trans-cutaneous, rectal, perlingual, ocular or respiratory administration and especially tablets, dragées, sublingual tablets, sachets, paquets, gelatin capsules, glossettes, lozenges, suppositories, creams, ointments, dermal gels and drinkable or injectable ampoules.

The dosage varies according to the sex, age and weight of the patient, the route of administration, the nature of the therapeutic indication, or possible associated treatments, and ranges from 0.01 mg to 1 g per 24 hours in 1 or more administrations.

The following Examples illustrate the invention but do not limit it in any way. The following Preparations yield compounds of the invention or synthesis intermediates that are useful in preparation of the compounds of the invention.

**Preparation 1 : 2-[7-(Methylthio)-1-naphthyl]-1-ethylamine hydrochloride**

*Step A :* 4-[4-(Methylthio)phenyl]-4-oxo-butanoic acid

Succinic anhydride (17 g, 170 mmol) is added to a solution of thioanisole (20 ml, 170 mmol) in 140 ml of tetrachloroethane and the reaction mixture is then brought to 0°C. Aluminium trichloride (45.43 g, 341 mmol) is added in portions and the reaction mixture is then heated at 60°C for 3.00 hours. After cooling and hydrolysis in the presence of ice-cold water (500 ml) and concentrated hydrochloric acid (50 ml), the white precipitate formed is filtered off, rinsed with water and recrystallised from ethyl acetate to yield the desired acid.

*Melting point = 153-155°C*

*Step B :* 4-[4-(Methylthio)phenyl]butanoic acid

A solution of the acid obtained in Step A (19.8 g, 88.1 mmol) in trifluoroacetic acid (68 ml, 881 mmol) is brought to 0°C and then triethylsilane hydride (35.2 ml, 220 mmol) is added dropwise using a dropping funnel. Stirring is carried out at ambient temperature for 17 hours. After hydrolysis, the white precipitate formed is filtered off, rinsed with water and with

cyclohexane and is then purified by chromatography on silica gel (eluant: acetone/toluene/cyclohexane 30/50/20) to yield the title compound.

*Melting point = 53-55°C*

*Step C :* 7-(Methylthio)-1,2,3,4-tetrahydro-1-naphthalenone

With the aid of a mechanical stirrer, the acid obtained in Step B (10 g, 52 mmol) is heated at 70°C for 2 hours in the presence of 10 times as much, by weight, polyphosphoric acid (100 g). The reaction mixture is hydrolysed in ice and is then extracted with ethyl ether. The organic phase is washed with water, dried over magnesium sulphate and evaporated. The residue is purified by chromatography on silica gel (eluant: dichloromethane) to yield the expected tetralone in the form of a yellow oil.

*Step D :* 2-[7-(Methylthio)-1,2,3,4-tetrahydro-1-naphthalenylidene]acetonitrile

Under an inert atmosphere and at 0°C, diethyl cyanomethylphosphonate (7.6 ml, 46.8 mmol) is added dropwise to a suspension of sodium hydride (2.25 g, 46.8 mmol) in 50 ml of tetrahydrofuran. Stirring is carried out at 0°C for 30 minutes; the compound obtained in Step C (6 g, 31.2 mmol), dissolved in 50 ml of tetrahydrofuran, is then added and the reaction mixture is stirred at ambient temperature for 3 hours. After hydrolysis and extraction with ethyl acetate, the organic phase is washed with water, dried over magnesium sulphate and evaporated. The residue is purified by chromatography on silica gel (eluant: petroleum ether/dichloromethane 50/50) to yield the unsaturated nitrile of the title.

*Melting point = 60-61°C*

*Step E :* 2-[7-(Methylthio)-1-naphthyl]acetonitrile

The compound obtained in Step D (2 g, 9.29 mmol) is heated at 230°C in the presence of sulphur (357 mg, 11.1 mmol) for 16 hours. After hydrolysis and extraction with ethyl acetate, the organic phase is washed with water, dried over magnesium sulphate and evaporated. The residue is purified by chromatography on silica gel (eluant: cyclohexane/ethyl acetate 80/20) to yield the corresponding aromatic compound in the form of a beige solid.

*Step F* : 2-[7-(Methylthio)-1-naphthyl]-1-ethylamine hydrochloride

Under an inert atmosphere, the compound obtained in Step E (1.93 g, 9.04 mmol), previously dissolved in 30 ml of tetrahydrofuran, is added to a 1M solution of borane in tetrahydrofuran (27.1 ml, 22.1 mmol) and the reaction mixture is then heated at reflux for 3 hours. A 6N hydrochloric acid solution (18 ml, 108 mmol) is then added very slowly and stirring is carried out at reflux for 30 minutes more. After extraction with ethyl acetate, the aqueous phase is rendered alkaline with 16 % sodium hydroxide solution and is then extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulphate and evaporated. The residue is purified by chromatography on silica gel (eluant: dichloromethane/methanol 50/50 and then methanol/ammonium hydroxide 95/5) to yield the expected amine. The amine is taken up in ethyl ether; ethyl ether saturated with gaseous hydrogen chloride is then added dropwise and the precipitate obtained is filtered off to yield the corresponding hydrochloride in the form of a white solid.

*Melting point = 199°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 61.52 | 6.35 | 5.52 |
| % found | 61.60 | 6.33 | 5.45 |

**Preparation 2 : N-[2-(7-Hydroxy-1-naphthyl)ethyl]acetamide**

Under an inert atmosphere, 27.5 mmol of boron tribromide/dimethyl sulphide complex are dissolved in 100 ml of dichloromethane and stirred for 15 min at ambient temperature. A solution of 13.7 mmol of N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide in 50 ml of dichloromethane is added and the reaction mixture is heated at reflux for 30 hours. After cooling, the reaction mixture is hydrolysed with caution and the dichloromethane is evaporated off. The mixture is then extracted with ethyl acetate, the combined organic phases are washed with a 1M aqueous solution of potassium bicarbonate and then with 1M sodium hydroxide solution. The organic phase is dried over magnesium sulphate and concentrated to yield the title compound.

**Preparation 3 : N-[2-(7-Hydroxy-1-naphthyl)ethyl]-2-phenylacetamide**

The procedure is as in Preparation 2, but the N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide is replaced by N-[2-(7-methoxy-1-naphthyl)ethyl]-2-phenylacetamide.

In Preparations 4 to 125, the procedure is as in Preparation 2, but the N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide is replaced by the appropriate methoxylated starting substrate.

**Preparation 4 : N-[2-(7-Hydroxy-1-naphthyl)ethyl]-2-(2-oxotetrahydro-*1H*-1-pyrrolyl)-acetamide**

**Preparation 5 : N-[2-(7-Hydroxy-1-naphthyl)ethyl]benzamide**

**Preparation 6 : N-[2-(7-Hydroxy-1-naphthyl)ethyl]-3-(trifluoromethyl)benzamide**

**Preparation 7 : N-[2-(7-Hydroxy-1-naphthyl)ethyl]-2-thiophenecarboxamide**

**Preparation 8 : N-[2-(7-Hydroxy-1-naphthyl)ethyl]-2-bromoacetamide**

**Preparation 9 : N-[2-(7-Hydroxy-1-naphthyl)ethyl]-4-chlorobutanamide**

**Preparation 10 : N-[2-(7-Hydroxy-1-naphthyl)ethyl]heptanamide**

**Preparation 11 : N-[2-(8-Allyl-7-hydroxy-1-naphthyl)ethyl]acetamide**

**Preparation 12 : N-[2-(8-Allyl-7-hydroxy-1-naphthyl)ethyl]heptanamide**

**Preparation 13 : N-{2-[7-Hydroxy-8-(1-propenyl)-1-naphthyl]ethyl}acetamide**

**Preparation 14 : N-{2-[7-Hydroxy-8-(1-propynyl)-1-naphthyl]ethyl}acetamide**

**Preparation 15 : N-[2-(8-Hexyl-7-hydroxy-1-naphthyl)ethyl]-2-phenylacetamide**

**Preparation 16 :** N-[2-(8-Allyl-7-hydroxy-1-naphthyl)ethyl]-N'-cyclobutylthiourea

**Preparation 17 :** N-Methyl-2-(7-hydroxy-1-naphthyl)acetamide

**Preparation 18 :** N-Cyclobutyl-3-(7-hydroxy-1-naphthyl)propanamide

**Preparation 19 :** N-Propyl-4-(7-hydroxy-1-naphthyl)butanamide

**Preparation 20 :** N-Cyclopropylmethyl-2-(7-hydroxy-1-naphthyl)acetamide

**Preparation 21 :** N-Cyclohexyl-4-(7-hydroxy-1-naphthyl)butanamide

**Preparation 22 :** N-Allyl-3-(7-hydroxy-1-naphthyl)propanamide

**Preparation 23 :** N-Cyclobutyl-N'-[2-(7-hydroxy-1-naphthyl)ethyl]urea

**Preparation 24 :** N-Isopropyl-N'-[2-(7-hydroxy-1-naphthyl)ethyl]thiourea

**Preparation 25 :** N-[2-(7-Hydroxy-1-naphthyl)ethyl]-N-methyl-N'-propylurea

**Preparation 26 :** N-Butyl-N'-[2-(7-hydroxy-1-naphthyl)ethyl]thiourea

**Preparation 27 :** N-Di(4-chlorophenyl)methyl-N'-[2-(7-hydroxy-1-naphthyl)ethyl]urea

**Preparation 28 :** Methyl 2-(7-hydroxy-1-naphthyl)-3-[(2-morpholinoacetyl)amino]-propanoate

**Preparation 29 :** Methyl 2-(7-hydroxy-1-naphthyl)-3-[(cyclopropylcarbonyl)amino]-propanoate

**Preparation 30 :** Methyl 2-(7-hydroxy-1-naphthyl)-3-[(2,2,2-trifluoroacetyl)amino]-propanoate

**Preparation 31 :** O-[(7-Hydroxy-1-naphthyl)methyl]-N-acetylhydroxylamine

**Preparation 32 :** O-[(7-Hydroxy-1-naphthyl)methyl]-N-(2-butenoyl)hydroxylamine

**Preparation 33 :** N-[3-(7-Hydroxy-1-naphthyl)propyl]acetamide

**Preparation 34 :** N-[3-(7-Hydroxy-1-naphthyl)propyl]-1-cyclohexanecarboxamide

**Preparation 35 :** N-[3-(7-Hydroxy-1-naphthyl)propyl]-N'-propylthiourea

**Preparation 36 :** N-[2-(2-Hydroxy-1-naphthyl)ethyl]-2,2,2-trifluoroacetamide

**Preparation 37 :** N-[2-(2-Hydroxy-1-naphthyl)ethyl]-2-butenamide

**Preparation 38 :** N-[2-(2-Hydroxy-1-naphthyl)ethyl]-1-cyclohexanecarboxamide

**Preparation 39 :** N-[2-(2-Hydroxy-1-naphthyl)-1-methylethyl]propanamide

**Preparation 40 :** N-[2-(7-Hydroxy-3-phenyl-1-naphthyl)ethyl]acetamide

**Preparation 41 :** N-[2-(3-Benzoyl-7-hydroxy-1-naphthyl)ethyl]acetamide

**Preparation 42 :** N-[2-(3-Benzoyl-7-hydroxy-1-naphthyl)ethyl]-N'-propylurea

**Preparation 43 :** N-{2-[3-(Cyclopropylcarbonyl)-7-hydroxy-1-naphthyl]ethyl}-1-cyclobutanecarboxamide

**Preparation 44 :** N-{2-[3-(Cyclopropylcarbonyl)-7-hydroxy-1-naphthyl]ethyl}-N'-propylurea

**Preparation 45 :** N-[2-(3,7-Dihydroxy-1-naphthyl)ethyl]propanamide

**Preparation 46 :** 4-{2-[(Cyclopropylcarbonyl)amino]ethyl}-6-hydroxy-2-naphthyl acetate

**Preparation 47 :** N-[2-(3-Benzyl-7-hydroxy-1-naphthyl)ethyl]pentanamide

**Preparation 48 :** N-[2-(3-Benzyl-7-hydroxy-1-naphthyl)ethyl]cyclohexanecarboxamide

**Preparation 49 :** N-Cyclohexyl-N'-[2-(3-ethyl-7-hydroxy-1-naphthyl)ethyl]urea

**Preparation 50 :** N-{2-[3-(Cyclopropylmethyl)-7-hydroxy-1-naphthyl]ethyl}acetamide

**Preparation 51 :** N-[(5-Hydroxybenzo[*b*]furan-3-yl)methyloxy]-N'-propylthiourea

**Preparation 52 :** N-[3-(5-Hydroxybenzo[*b*]furan-3-yl)propyl]acetamide

**Preparation 53 :** N-[2-(5-Hydroxy-2-methylbenzo[*b*]furan-3-yl)ethyl]heptanamide

**Preparation 54 :** N-Methyl-4-(5-hydroxybenzo[*b*]furan-3-yl)butanamide

**Preparation 55 :** N-[2-(4-Allyl-5-hydroxybenzo[*b*]furan-3-yl)ethyl]benzamide

**Preparation 56 :** N-[2-(5-Hydroxybenzo[*b*]furan-3-yl)ethyl]acetamide

**Preparation 57 :** O-[(5-Hydroxybenzo[*b*]thiophen-3-yl)methyl]-N-thiopropionyl-hydroxylamine

**Preparation 58 :** N-[3-(5-Hydroxybenzo[*b*]thiophen-3-yl)propyl]-1-cyclopropane-carboxamide

**Preparation 59 :** N-[(2-Benzyl-5-hydroxybenzo[*b*]thiophen-3-yl)methyl]acetamide

**Preparation 60 :** N-[2-(5-Hydroxythieno[*3,2-b*]pyridin-3-yl)ethyl]acetamide

**Preparation 61 :** N-[2-(4-Allyl-5-hydroxybenzo[*b*]thiophen-3-yl)ethyl]benzamide

**Preparation 62 :** N-[2-(5-Hydroxy-*1H*-4-indolyl)ethyl]-1-cyclopropanecarboxamide

**Preparation 63 :** N-Methyl-4-(5-hydroxybenzo-*1H*-3-indolyl)butanamide

**Preparation 64 :** N-[2-(5-Hydroxy-*1H*-3-indolyl)ethyl]-2-morpholinoacetamide

**Preparation 65 :** N-Benzyl-N'-[2-(5-hydroxy-*1H*-3-indolyl)ethyl]urea

**Preparation 66 :** N-[2-(5-Hydroxy-*1H*-3-indolyl)ethyl]benzamide

**Preparation 67 :** N-[2-(5-Hydroxy-1-methyl-2-phenyl-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl)-ethyl]acetamide

**Preparation 68 :** N-{2-[5-Hydroxy-2-(2-methoxyphenyl)-1-methyl-*1H*-pyrrolo[*2,3-b*]-pyridin-3-yl]ethyl}acetamide

**Preparation 69 :** N-{2-[2-(4-Fluorobenzyl)-5-hydroxy-1-methyl-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl]ethyl}acetamide

**Preparation 70 :** N-[2-(2-Benzyl-5-hydroxy-1-methyl-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl]-ethyl}acetamide

**Preparation 71 :** N-[2-(5-Hydroxy-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl)ethyl]acetamide

**Preparation 72 :** N-[2-(5-Hydroxy-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl)ethyl]trifluoroacetamide

**Preparation 73 :** N-[2-(5-Hydroxy-2-phenyl-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl)ethyl]-acetamide

**Preparation 74 :** N-[2-(5-Hydroxy-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl)ethyl]-N'-propylurea

**Preparation 75 :** N-[2-(5-Hydroxy-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl)ethyl]cyclobutane-carboxamide

**Preparation 76 :** N-[2-(5-Hydroxy-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl)ethyl]-N'-butylthiourea

**Preparation 77 :** N-[2-(2-Benzyl-5-hydroxybenzo[*b*]furan-3-yl)ethyl]-1-cyclopropane-carboxamide

**Preparation 78 :** N-[2-(6-Hydroxy-*1H*-benzo-imidazol-1-yl)ethyl]-1-cyclopropane-carboxamide

**Preparation 79 :** N-[(6-Hydroxy-3,4-dihydro-*2H*-3-chromenyl)methyl]acetamide

**Preparation 80 :** N-[(6-Hydroxy-3,4-dihydro-*2H*-3-chromenyl)methyl]cyclopropane-carboxamide

**Preparation 81 :** N-[2-(6-Hydroxy-3,4-dihydro-*2H*-3-chromenyl)ethyl]acetamide

**Preparation 82 :** N-[(6-Hydroxy-3,4-dihydro-*2H*-4-chromenyl)methyl]acetamide

**Preparation 83 :** N-[(6-Hydroxy-3,4-dihydro-*2H*-3-chromenyl)methyl]butanamide

**Preparation 84 :** N-[2-(6-Hydroxy-3,4-dihydro-*2H*-4-chromenyl)ethyl]-3-butenamide

**Preparation 85 :** N-[2-(6-Hydroxy-3,4-dihydro-*2H*-4-chromenyl)ethyl]acetamide

**Preparation 86 :** N-[2-(6-Hydroxy-3,4-dihydro-*2H*-4-chromenyl)ethyl]-2-phenylacetamide

**Preparation 87** : N-[(6-Hydroxy-*2H*-3-chromenyl)methyl]acetamide

**Preparation 88** : N-[(6-Hydroxy-*2H*-3-chromenyl)methyl]butanamide

**Preparation 89** : N-Methyl-3-(6-hydroxy-*2H*-3-chromenyl)propanamide

**Preparation 90** : N-[(6-Hydroxy-2-phenyl-*2H*-3-chromenyl)methyl]acetamide

**Preparation 91** : N-[(6-Hydroxy-2-phenyl-*2H*-3-chromenyl)methyl]butanamide

**Preparation 92** : N-[2-(6-Hydroxy-3,4-dihydro-*2H*-4-thiochromenyl)ethyl]acetamide

**Preparation 93** : N-[(7-Hydroxy-3-phenyl-1,4-benzodioxin-2-yl)methyl]acetamide

**Preparation 94** : N-[(3-Benzyl-7-hydroxy-1,4-benzodioxin-2-yl)methyl]acetamide

**Preparation 95** : N-[(7-Hydroxy-1,4-benzodioxin-2-yl)methyl]cyclopropanecarboxamide

**Preparation 96** : N-[2-(7-Hydroxy-1,4-benzodioxin-2-yl)ethyl-N'-propylurea

**Preparation 97** : N-[2-(7-Hydroxy-2,3-dihydro-1,4-benzodioxin-2-yl)ethyl]acetamide

**Preparation 98** : N-Phenyl-2-(7-hydroxy-2,3-dihydro-1,4-benzodioxin-2-yl)acetamide

**Preparation 99** : N-[2-(6-Hydroxy-2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]acetamide

**Preparation 100** : N-[3-(7-Hydroxy-1,2,3,4-tetrahydro-1-naphthyl)propyl]acetamide

**Preparation 101** : N-[2-(5-Hydroxybenzo[*d*]isoxazol-3-yl)ethyl]-1-cyclopropane-carboxamide

**Preparation 102** : N-(9-Hydroxy-2,3-dihydro-*1H*-benzo[*f*]chromen-2-yl)acetamide

**Preparation 103** : N-[(9-Hydroxy-2,3-dihydro-*1H*-benzo[*f*]chromen-2-yl)methyl]-2-cyclopropylacetamide

**Preparation 104** : N-(9-Hydroxy-2,3-dihydro-*1H*-benzo[*f*]chromen-1-yl)butanamide

**Preparation 105** : N-[(9-Hydroxy-2,3-dihydro-*1H*-benzo[*f*]chromen-1-yl)methyl]acetamide

**Preparation 106** : N-Methyl-9-hydroxy-*3H*-benzo[*f*]chromene-2-carboxamide

**Preparation 107** : N-(4-Hydroxy-2,3-dihydro-*1H*-2-phenalenyl)propanamide

**Preparation 108** : N-(4-Hydroxy-2,3-dihydro-*1H*-2-phenalenyl)-2-methylpropanamide

**Preparation 109** : N-Cyclopropyl-N'-(4-hydroxy-2,3-dihydro-*1H*-2-phenalenyl)thiourea

**Preparation 110** : N-Cyclohexyl-N'-(4-hydroxy-2,3-dihydro-*1H*-2-phenalenyl)urea

**Preparation 111** : N-(4,9-Dihydroxy-2,3-dihydro-*1H*-2-phenalenyl)acetamide

**Preparation 112** : N-[(4-Hydroxy-2,3-dihydro-*1H*-1-phenalenyl)methyl]acetamide

**Preparation 113** : N-[2-(4-Hydroxy-2,3-dihydro-*1H*-1-phenalenyl)ethyl]-1-cyclopropane-carboxamide

**Preparation 114** : N-[(4,9-Dihydroxy-2,3-dihydro-*1H*-1-phenalenyl)methyl]-N'-methylurea

**Preparation 115** : N-(6-Hydroxy-1,3,4,5-tetrahydrobenzo[*cd*]indol-4-yl)acetamide

**Preparation 116** : N-(6-Hydroxy-4,5-dihydro-*3H*-benzo[*cd*]isobenzofuran-4-yl)acetamide

**Preparation 117** : **N-(6-Hydroxy-4,5-dihydro-*3H*-naphtho[*1,8-bc*]thiophen-4-yl)acetamide**

**Preparation 118** : **N-Cyclobutyl-3-hydroxy-4,5-dihydro-*3H*-benzo[*cd*]isobenzofuran-4-carboxamide**

**Preparation 119** : **N-{[2-(2-Furylmethyl)-5-hydroxybenzo[*b*]furan-3-yl]methyl}acetamide**

**Preparation 120** : **N-{[5-Hydroxy-2-(3-pyridylmethyl)benzo[*b*]furan-3-yl]methyl}-benzamide**

**Preparation 121** : **N-{[5-Hydroxy-2-(3-phenyl-2-propenyl)benzo[*b*]thiophen-3-yl]methyl}-1-cyclobutanecarboxamide**

**Preparation 122** : **N-{2-[7-Hydroxy-3-naphthyl-1-naphthyl]ethyl}heptanamide**

**Preparation 123** : **4-[2-(Benzoylamino)ethyl]-6-hydroxy-2-naphthyl trifluoromethane-sulphonate**

**Preparation 124** : **N-{2-[7-Hydroxy-3-(3-phenyl-2-propenyl)-1-naphthyl]ethyl}-2-phenylacetamide**

**Preparation 125** : **N-{[7-Hydroxy-3-(2-thienyl)-1-naphthyl]methyl}butanamide**

**Preparation 126** : **N-[2-(7-Chloro-1-naphthyl)ethyl]benzamide**

Chlorine (10 mmol) is bubbled into dichlorophenylphosphine at a flow rate such that the reaction temperature is maintained between 70 and 80°C. After all the chlorine has been added, the phenylphosphine tetrachloride so obtained is a pale yellow liquid. 10 mmol of the product obtained in Preparation 5 are added all at once and the reaction mixture is heated at 160°C overnight. After cooling, the solution is poured into a water/ice mixture (20 ml) and is neutralised with a 50 % aqueous solution of sodium hydroxide. After extraction with ether, the

organic phases are dried and concentrated under reduced pressure to yield a residue, which is chromatographed on silica gel to obtain the pure title product.

In Preparations 127 to 133, the procedure is as in Preparation 126, but the appropriate starting compound is used.

**Preparation 127 : N-{2-[7-Chloro-8-(1-propenyl)-1-naphthyl]ethyl}acetamide**

*Starting compound : Preparation 13*

**Preparation 128 : N-Cyclohexyl-4-(7-chloro-1-naphthyl)butanamide**

*Starting compound : Preparation 21*

**Preparation 129 : N-[2-(7-Chloro-3-ethyl-1-napthyl)ethyl]-N'-cyclohexylurea**

*Starting compound : Preparation 49*

**Preparation 130 : N-[2-(5-Chloro-*1H*-4-indolyl)ethyl-1-cyclopropanecarboxamide**

*Starting compound : Preparation 62*

**Preparation 131 : N-[(6-Chloro-3,4-dihydro-*2H*-3-chromenyl)methyl]acetamide**

*Starting compound : Preparation 79*

**Preparation 132 : N-(9-Chloro-2,3-dihydro-*1H*-benzo[*f*]chromen-2-yl)acetamide**

*Starting compound : Preparation 102*

**Preparation 133 : N-(4-Chloro-2,3-dihydro-*1H*-2-phenalenyl)-N'-cyclohexylurea**

*Starting compound : Preparation 110*

**Preparation 134 : N-[2-(7-Bromo-1-naphthyl)ethyl]-2-phenylacetamide**

Triphenylphosphine (10 mmol) and acetonitrile (70 ml) are poured into a 150 ml three-necked flask equipped with a bromine funnel, a condenser surmounted by a tube filled with calcium chloride and a mechanical stirrer. The solution is cooled with the aid of an ice bath, with stirring,

and bromine is added (10 mmol). At the end of the addition, the ice bath is removed and the product obtained in Preparation 3 (8 mmol) is then added. The reaction mixture is stirred at 60-70°C until the starting compound has disappeared (monitored by TLC). At the end of the reaction, the mixture is filtered and the filtrate is then concentrated under reduced pressure. The residue is taken up in ethyl acetate, washed with water and then with saturated potassium hydrogen carbonate solution and once again with water, and is then dried over magnesium sulphate and concentrated under reduced pressure. The residue is filtered through silica gel to yield the title product.

In Preparations 135 to 159, the procedure is as in Preparation 134, starting from the appropriate reactant.

**Preparation 135 : N-[2-(8-Allyl-7-bromo-1-naphthyl)ethyl]-N'-cyclobutylthiourea**

*Starting compound : Preparation 16*

**Preparation 136 : N-Cyclopropylmethyl-2-(7-bromo-1-naphthyl)acetamide**

*Starting compound : Preparation 20*

**Preparation 137 : N-[2-(7-Bromo-1-naphthyl)ethyl]-N-methyl-N'-propylurea**

*Starting compound : Preparation 25*

**Preparation 138 : Methyl 2-(7-bromo-1-naphthyl)-3-[(2,2,2-trifluoroacetyl)amino]-propanoate**

*Starting compound : Preparation 30*

**Preparation 139 : N-[3-(7-Bromo-1-naphthyl)propyl]-1-cyclohexanecarboxamide**

*Starting compound : Preparation 34*

**Preparation 140 : N-[2-(2-Bromo-1-naphthyl)ethyl]-2,2,2-trifluoroacetamide**

*Starting compound : Preparation 36*

**Preparation 141** : **N-[2-(3-Benzoyl-7-bromo-1-naphthyl)ethyl]-N'-propylurea**

*Starting compound : Preparation 42*

**Preparation 142** : **N-[3-(5-Bromobenzo[*b*]furan-3-yl)propyl]acetamide**

*Starting compound : Preparation 52*

**Preparation 143** : **N-[(2-Benzyl-5-bromobenzo[*b*]thiophen-3-yl)methyl]acetamide**

*Starting compound : Preparation 59*

**Preparation 144** : **N-[2-(4-Allyl-5-bromobenzo[*b*]thiophen-3-yl)ethyl]benzamide**

*Starting compound : Preparation 61*

**Preparation 145** : **N-[2-(5-Bromo-*1H*-3-indolyl)ethyl]-2-morpholinoacetamide**

*Starting compound : Preparation 64*

**Preparation 146** : **N-[2-(5-Bromo-2-(4-fluorobenzyl)-1-methyl-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl)ethyl]acetamide**

*Starting compound : Preparation 69*

**Preparation 147** : **N-[2-(6-Bromo-*1H*-benzo[*b*]imidazol-1-yl)ethyl]-1-cyclopropane-carboxamide**

*Starting compound : Preparation 78*

**Preparation 148** : **N-[(6-Bromo-3,4-dihydro-*2H*-3-chromenyl)methyl]acetamide**

*Starting compound : Preparation 79*

**Preparation 149** : **N-[2-(6-Bromo-3,4-dihydro-*2H*-4-chromenyl)ethyl]-2-phenylacetamide**

*Starting compound : Preparation 86*

**Preparation 150** : **N-[(6-Bromo-2-phenyl-*2H*-3-chromenyl)methyl]acetamide**

*Starting compound : Preparation 90*

**Preparation 151** : **N-[2-(6-Bromo-3,4-dihydro-*2H*-4-thiochromenyl)ethyl]acetamide**

*Starting compound : Preparation 92*

**Preparation 152** : **N-[2-(7-Bromo-1,4-benzodioxin-2-yl)ethyl]-N'-propylurea**

*Starting compound : Preparation 96*

**Preparation 153** : **N-[2-(6-Bromo-2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]acetamide**

*Starting compound : Preparation 99*

**Preparation 154** : **N-[(9-Bromo-2,3-dihydro-*1H*-benzo[*f*]chromen-2-yl)methyl]-2-cyclopropylacetamide**

*Starting compound : Preparation 103*

**Preparation 155** : **N-(4-Bromo-2,3-dihydro-*1H*-2-phenalenyl)-N'-cyclopropylthiourea**

*Starting compound : Preparation 109*

**Preparation 156** : **N-(6-Bromo-1,3,4,5-tetrahydrobenzo[*cd*]indol-4-yl)acetamide**

*Starting compound : Preparation 115*

**Preparation 157** : **N-Cyclobutyl-6-bromo-4,5-dihydro-*3H*-benzo[*cd*]isobenzofuran-4-carboxamide**

*Starting compound : Preparation 118*

**Preparation 158** : **N-[2-(7-Bromo-3-naphthyl)ethyl]heptanamide**

*Starting compound : Preparation 122*

**Preparation 159** : **N-{2-[7-Bromo-3-(3-phenyl-2-propenyl)-1-naphthyl])ethyl}-2-cyclohexyl-acetamide**

*Starting compound : Preparation 124*

**Preparation 160 : N-[2-(7-Iodo-1-naphthyl)ethyl]-2-phenylacetamide**

A mixture of the product obtained in Preparation 134 (2 mmol), potassium iodide (30 mmol) and copper(I) iodide (10 mmol) in hexamethylphosphoramide (6 ml) is heated at 150-160°C, with stirring, under a nitrogen atmosphere until 90 % conversion has been achieved (monitored by TLC). Then, dilute hydrochloric acid, and then ether, are added and the mixture is then filtered to remove the insoluble copper(I) salts. The organic phase is separated off, washed with sodium sulphite solution and with water, dried over magnesium sulphate and evaporated to yield a residue which is chromatographed on silica gel to yield the title product.

In Preparations 161 to 185 the procedure is as in Preparation 160, but the product of Preparation 134 is replaced by the appropriate substrate.

**Preparation 161 : N-[2-(8-Allyl-7-iodo-1-naphthyl)ethyl]-N'-cyclobutylthiourea**

*Starting compound : Preparation 135*

**Preparation 162 : N-Cyclopropylmethyl-2-(7-iodo-1-naphthyl)acetamide**

*Starting compound : Preparation 136*

**Preparation 163 : N-[2-(7-Iodo-1-naphthyl)ethyl]-N-methyl-N'-propylurea**

*Starting compound : Preparation 137*

**Preparation 164 : Methyl 2-(7-iodo-1-naphthyl)-3-[(2,2,2-trifluoroacetyl)amino]propanoate**

*Starting compound : Preparation 138*

**Preparation 165 : N-[3-(7-Iodo-1-naphthyl)propyl]-1-cyclohexanecarboxamide**

*Starting compound : Preparation 139*

**Preparation 166 : N-[2-(2-Iodo-1-naphthyl)ethyl]-2,2,2-trifluoroacetamide**

*Starting compound : Preparation 140*

**Preparation 167** : **N-[2-(3-Benzoyl-7-iodo-1-naphthyl)ethyl]-N'-propylurea**

*Starting compound : Preparation 141*

**Preparation 168** : **N-[3-(5-Iodobenzo[*b*]furan-3-yl)propyl]acetamide**

*Starting compound : Preparation 142*

**Preparation 169** : **N-[(2-Benzyl-5-iodobenzo[*b*]thiophen-3-yl)methyl]acetamide**

*Starting compound : Preparation 143*

**Preparation 170** : **N-[2-(4-Allyl-5-iodobenzo[*b*]thiophen-3-yl)ethyl]benzamide**

*Starting compound : Preparation 144*

**Preparation 171** : **N-[2-(5-Iodo-*1H*-3-indolyl)ethyl]-2-morpholinoacetamide**

*Starting compound : Preparation 145*

**Preparation 172** : **N-[2-(5-Iodo-2-(4-fluorobenzyl)-1-methyl-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl)-ethyl]acetamide**

*Starting compound : Preparation 146*

**Preparation 173** : **N-[2-(6-Iodo-*1H*-benzo[*d*]imidazol-1-yl)ethyl]-1-cyclopropane-carboxamide**

*Starting compound : Preparation 147*

**Preparation 174** : **N-[(6-Iodo-3,4-dihydro-*2H*-3-chromenyl)methyl]acetamide**

*Starting compound : Preparation 148*

**Preparation 175** : **N-[2-(6-Iodo-3,4-dihydro-*2H*-4-chromenyl)ethyl]-2-phenylacetamide**

*Starting compound : Preparation 149*

**Preparation 176** : **N-[(6-Iodo-2-phenyl-*2H*-3-chromenyl)methyl]acetamide**

*Starting compound : Preparation 150*

**Preparation 177** : **N-[2-(6-Iodo-3,4-dihydro-*2H*-4-thiochromenyl)ethyl]acetamide**

*Starting compound : Preparation 151*

**Preparation 178** : **N-[2-(7-Iodo-1,4-benzodioxin-2-yl)ethyl]-N'-propylurea**

*Starting compound : Preparation 152*

**Preparation 179** : **N-[2-(6-Iodo-2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]acetamide**

*Starting compound : Preparation 153*

**Preparation 180** : **N-[(9-Iodo-2,3-dihydro-*1H*-benzo[*f*]chromen-2-yl)methyl]-2-cyclopropyl-acetamide**

*Starting compound : Preparation 154*

**Preparation 181** : **N-(4-Iodo-2,3-dihydro-*1H*-2-phenalenyl)-N'-cyclopropylthiourea**

*Starting compound : Preparation 155*

**Preparation 182** : **N-(6-Iodo-1,3,4,5-tetrahydrobenzo[*cd*]indol-4-yl)acetamide**

*Starting compound : Preparation 156*

**Preparation 183** : **N-Cyclobutyl-6-iodo-4,5-dihydro-*3H*-benzo[*cd*]isobenzofuran-4-carboxamide**

*Starting compound : Preparation 157*

**Preparation 184** : **N-[2-(7-Iodo-3-naphthyl-1-naphthyl)ethyl]heptanamide**

*Starting compound : Preparation 158*

**Preparation 185** : **N-{2-[7-Iodo-3-(3-phenylpropenyl)-1-naphthyl]ethyl}-2-cyclohexyl-acetamide**

*Starting compound : Preparation 159*

In Preparations 186 to 197 the procedure is as in Preparation 134, starting from the appropriate substrate.

**Preparation 186** : **N-[2-(7-Bromo-1-naphthyl)ethyl]-2-bromoacetamide**

*Starting compound : Preparation 8*

**Preparation 187** : **N-[2-(7-Bromo-8-hexyl-1-naphthyl)ethyl]-2-phenylacetamide**

*Starting compound : Preparation 15*

**Preparation 188** : **N-Cyclohexyl-4-(7-bromo-1-naphthyl)butanamide**

*Starting compound : Preparation 21*

**Preparation 189** : **N-[3-(7-Bromo-1-naphthyl)propyl]acetamide**

*Starting compound : Preparation 33*

**Preparation 190** : **N-[2-(2-Bromo-1-naphthyl)-1-methylethyl]propanamide**

*Starting compound : Preparation 39*

**Preparation 191** : **N-{2-[7-Bromo-3-(cyclopropylmethyl)-1-naphthyl]ethyl}acetamide**

*Starting compound : Preparation 50*

**Preparation 192** : **N-Methyl-3-(5-bromobenzo[*b*]furan-3-yl)butanamide**

*Starting compound : Preparation 54*

**Preparation 193** : **N-[2-(5-Bromothieno[*3,2-b*]pyridin-3-yl)ethyl]acetamide**

*Starting compound : Preparation 60*

**Preparation 194** : **N-[2-(5-Bromo-*1H*-3-indolyl)ethyl]benzamide**

*Starting compound : Preparation 66*

**Preparation 195** : **N-[2-(2-Benzyl-5-bromobenzo[*b*]furan-3-yl)ethyl]-1-cyclopropane-carboxamide**

*Starting compound : Preparation 77*

**Preparation 196** : **N-[(6-Bromo-2-phenyl-*2H*-3-chromenyl)methyl]butanamide**

*Starting compound : Preparation 91*

**Preparation 197** : **N-(4,9-Dibromo-2,3-dihydro-*1H*-2-phenalenyl)acetamide**

*Starting compound : Preparation 111*

In Preparations 198 to 209 the procedure is as in Preparation 160, starting from the appropriate substrate.

**Preparation 198** : **N-[2-(7-Iodo-1-naphthyl)ethyl]-2-bromoacetamide**

*Starting compound : Preparation 186*

**Preparation 199** : **N-[2-(7-Iodo-8-hexyl-1-naphthyl)ethyl]-2-phenylacetamide**

*Starting compound : Preparation 187*

**Preparation 200** : **N-Cyclohexyl-4-(7-iodo-1-naphthyl)butanamide**

*Starting compound : Preparation 188*

**Preparation 201** : **N-[3-(7-Iodo-1-naphthyl)propyl]acetamide**

*Starting compound : Preparation 189*

**Preparation 202** : **N-[2-(2-Iodo-1-naphthyl)-1-methylethyl]propanamide**

*Starting compound : Preparation 190*

**Preparation 203** : **N-{2-[7-Iodo-3-(cyclopropylmethyl)-1-naphthyl]ethyl}acetamide**

*Starting compound : Preparation 191*

**Preparation 204** : **N-Methyl-4-(5-iodobenzo[*b*]furan-3-yl)butanamide**

*Starting compound : Preparation 192*

**Preparation 205** : **N-[2-(5-Iodothieno[*3,2-b*]pyridin-3-yl)ethyl]acetamide**

*Starting compound : Preparation 193*

**Preparation 206** : **N-[2-(5-Iodo-*1H*-3-indolyl)ethyl]benzamide**

*Starting compound : Preparation 194*

**Preparation 207** : **N-[2-(2-Benzyl-5-iodobenzo[*b*]furan-3-yl)ethyl]-1-cyclopropane-carboxamide**

*Starting compound : Preparation 195*

**Preparation 208** : **N-[(6-Iodo-2-phenyl-*2H*-3-chromenyl)methyl]butanamide**

*Starting compound : Preparation 196*

**Preparation 209** : **N-[4,9-Diiodo-2,3-dihydro-*1H*-2-phenalenyl)acetamide**

*Starting compound : Preparation 197*

In Preparations 210 to 223 the procedure is as in Preparation 2.

**Preparation 210** : **N-[2-(5-Hydroxy-2-phenylbenzo[*b*]thiophen-3-yl)ethyl]acetamide**

**Preparation 211** : **N-[2-(5-Hydroxybenzo[*b*]thiophen-3-yl)ethyl]acetamide**

**Preparation 212** : **N-[2-(5-Hydroxybenzo[*b*]thiophen-3-yl)ethyl]acrylamide**

**Preparation 213** : **N-[2-(5-Hydroxybenzo[*b*]thiophen-3-yl)ethyl]-2,2,2-trifluoroacetamide**

**Preparation 214** : **N-[2-(5-Hydroxybenzo[*b*]thiophen-3-yl)ethyl]-1-cyclopropane-carboxamide**

**Preparation 215** : **N-[2-(5-Hydroxybenzo[*b*]thiophen-3-yl)ethyl]butanamide**

**Preparation 216** : **N-[2-(5-Hydroxybenzo[*b*]thiophen-3-yl)ethyl]-N'-methylurea**

**Preparation 217** : **N-[2-(5-Hydroxybenzo[*b*]thiophen-3-yl)ethyl]benzamide**

**Preparation 218 : N-[2-(5-Hydroxybenzo[*b*]thiophen-3-yl)ethyl]-2-(3,4-dichlorophenyl)-acetamide**

**Preparation 219 : N-[2-(7-Hydroxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl]acetamide**

**Preparation 220 : N-(8-Hydroxy-5-methyl-1,2,3,4-tetrahydro-2-naphthyl)acetamide**

**Preparation 221 : N-2,5-Dimethyl-8-hydroxy-1,2,3,4-tetrahydro-2-naphthalenecarboxamide**

**Preparation 222 : N-[2-(5-Hydroxybenzo[*b*]thiophen-3-yl)ethyl]-3-butenamide**

**Preparation 223 : N-[2-(6-Hydroxy-2,3-dihydro-*1H*-1-indenyl)ethyl]acetamide**

**Preparation 224 : N-[2-(5-Chloro-2-phenylbenzo[*b*]thiophen-3-yl)ethyl]acetamide**

*Step A* : 1-[(4-Chlorophenyl)thio]-1-phenylacetone

In a 100 ml round-bottomed flask, 1 eq. of 4-chlorothiophenol is dissolved in 4 eq. of pyridine and 50 ml of anhydrous ether, with magnetic stirring. 1.2 eq. of bromophenylacetone are then added dropwise and stirring is then carried out overnight at ambient temperature. The reaction mixture is then poured onto ice-cold water and is extracted with ethyl acetate. The organic phase is washed with 1M HCl solution and then with water, is dried over $MgSO_4$ and is evaporated under reduced pressure. The residue obtained is purified by chromatography on a silica gel column.

*Step B* : 5-Chloro-3-methyl-2-phenyl-1-benzothiophene

In a 100 ml round-bottomed flask, 1 eq. of the compound obtained in Step A, 10 eq. of polyphosphoric acid and 1 eq. of phosphoric anhydride are mixed together. The mixture is stirred for 3 hours at 180°C and is then hydrolysed. Extraction with ether is carried out, and the organic

phase is washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue obtained is purified by chromatography on a silica gel column.

*Melting point = 108-109°C*

*Step C :* 3-(Bromomethyl)-5-chloro-2-phenyl-1-benzothiophene

In a 100 ml round-bottomed flask, 1 eq. of the compound obtained in Step B is dissolved in 20 ml of $CCl_4$. 1 eq. of N-bromosuccinimide and 0.04 eq. of benzoyl peroxide are then added, and the mixture is irradiated by means of a halogen lamp and maintained at reflux for 4 hours. At the end of the reaction, the insoluble material is filtered off, and the carbon tetrachloride is evaporated off. The residue obtained is purified by chromatography on a silica gel column.

*Melting point = 128-129°C*

*Step D :* 2-(5-Chloro-2-phenyl-1-benzothiophen-3-yl)acetonitrile

1.2 eq. of NaCN are suspended in 20 ml of dimethyl sulphoxide. The mixture is heated at 60°C for 30 minutes and then 1 eq. of the compound obtained in Step C is added gradually. The reaction mixture is stirred for 1 hour at 60°C and is then hydrolysed. Extraction with ethyl acetate is carried out and the organic phase is washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue obtained is purified by chromatography on silica gel.

*Melting point = 156-157°C*

*Step E :* 2-(5-Chloro-2-phenyl-1-benzothiophen-3-yl)-1-ethanamine hydrochloride

3 eq. of diborane in tetrahydrofuran and 1 eq. of the nitrile obtained in Step D are introduced into a 100 ml round-bottomed flask, and the mixture is then heated at reflux for 2 hours. After cooling, 15 eq. of 6M HCl are added and the tetrahydrofuran is evaporated off under reduced pressure. The precipitate formed is filtered off and recrystallised.

*Melting point = 291-292°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 52.12 | 4.10 | 3.78 |
| % found | 52.48 | 4.42 | 3.37 |

*Step F :* N-[2-(5-Chloro-2-phenylbenzo[*b*]thiophen-3-yl)ethyl]acetamide

The compound obtained in Step E is dissolved in a mixture of water/dichloromethane (2/3); 2 eq. of potassium carbonate are then added and 2 eq. acetyl chloride are added dropwise. After stirring for 2 hours at ambient temperature, the 2 phases are separated; the organic phase is washed with 1M HCl and then with water, until the washing waters are neutral, and is then dried over $MgSO_4$ and evaporated. The residue obtained is purified by chromatography on silica gel.

*Melting point = 147-149°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 65.54 | 4.89 | 4.25 |
| % found | 65.55 | 4.90 | 4.25 |

Preparations 225 to 235 are obtained by proceeding as in Preparation 224.

**Preparation 225 : N-[2-(5-Chlorobenzo[*b*]thiophen-3-yl)ethyl]acetamide**

*Melting point = 129-130°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 56.80 | 4.77 | 5.52 |
| % found | 56.73 | 4.72 | 5.44 |

**Preparation 226 : N-[2-(5-Chlorobenzo[*b*]thiophen-3-yl)ethyl]acrylamide**

*Melting point = 111-113°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 58.75 | 4.55 | 5.27 |
| % found | 58.65 | 4.58 | 5.14 |

**Preparation 227 : N-[2-(5-Chlorobenzo[*b*]thiophen-3-yl)ethyl]-2,2,2-trifluoroacetamide**

*Melting point = 132-134°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 46.83 | 2.95 | 4.55 |
| % found | 47.10 | 2.99 | 4.47 |

**Preparation 228 : N-[2-(5-Chlorobenzo[*b*]thiophen-3-yl)ethyl]-1-cyclopropanecarboxamide**

*Melting point = 161-163°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 60.10 | 5.04 | 5.01 |
| % found | 60.23 | 5.14 | 4.93 |

**Preparation 229 : N-[2-(5-Bromobenzo[*b*]thiophen-3-yl)ethyl]acetamide**

*Melting point = 134-136°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 48.33 | 4.06 | 4.70 |
| % found | 48.65 | 4.14 | 4.72 |

**Preparation 230 : N-[2-(5-Bromobenzo[*b*]thiophen-3-yl)ethyl]-2,2,2-trifluoroacetamide**

*Melting point = 144.5-145.5°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 40.92 | 2.58 | 3.98 |
| % found | 41.09 | 2.66 | 4.05 |

**Preparation 231** : **N-[2-(5-Bromobenzo[*b*]thiophen-3-yl)ethyl]butanamide**

*Melting point = 124-125°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 51.54 | 4.94 | 4.29 |
| % found | 51.41 | 5.01 | 4.35 |

**Preparation 232** : **N-[2-(5-Bromobenzo[*b*]thiophen-3-yl)ethyl]-N'-methylurea**

*Melting point = 174-178°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 46.01 | 4.18 | 8.94 |
| % found | 45.64 | 4.17 | 8.86 |

**Preparation 233** : **N-[2-(5-Bromobenzo[*b*]thiophen-3-yl)ethyl]benzamide**

*Melting point = 142-145°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 56.67 | 3.92 | 3.89 |
| % found | 56.76 | 3.94 | 3.82 |

**Preparation 234** : **N-[2-(5-Bromobenzo[*b*]thiophen-3-yl)ethyl]-2-(3,4-dichlorophenyl)-acetamide**

*Melting point = 170-171°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 48.78 | 3.18 | 3.16 |
| % found | 48.88 | 3.20 | 3.38 |

**Preparation 235** : **N-[2-(5-Bromobenzo[*b*]thiophen-3-yl)ethyl]-3-butenamide**

*Melting point = 90-91°C*

Preparations 236 to 238 are obtained by proceeding as in Preparation 134.

**Preparation 236 : N-[2-(7-Bromo-1,2,3,4-tetrahydro-1-naphthyl)ethyl]acetamide**

**Preparation 237 : N-(8-Bromo-5-methyl-1,2,3,4-tetrahydro-2-naphthyl)acetamide**

**Preparation 238 : N-2,5-Dimethyl-8-bromo-1,2,3,4-tetrahydro-2-naphthalenecarboxamide**

**Preparation 239 : N-[2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthyl)ethyl]acetamide**

*Step A :* 4-(4-Fluorophenyl)-4-oxobutanoic acid

0.4 mol of aluminium chloride and 94 ml of fluorobenzene are introduced into a 500 ml flask with a ground neck and then 0.2 mol of succinic anhydride is added in small portions, with magnetic stirring. The mixture is heated at 60°C for 5 hours and is then cooled and poured into ice-cold water. After acidification using 3M HCl solution, the precipitate formed is filtered off under suction, washed with cyclohexane and recrystallised.
*Melting point = 102-103°C*

*Step B :* Methyl 4-(4-fluorophenyl)-4-oxobutanoate

In a 500 ml round-bottomed flask, 0.092 mol of the compound obtained in Step A is dissolved in 200 ml of methanol The mixture is cooled using an ice bath and 0.138 mol of thionyl chloride is added dropwise. The reaction mixture is stirred for 5 hours at ambient temperature; the methanol is then evaporated off and the solid obtained is taken up in petroleum ether, filtered off under suction and used directly in the following Step.

*Step C :* Methyl 4-(4-fluorophenyl)butanoate

In a 500 ml round-bottomed flask, 0.095 mol of the compound obtained in Step B is dissolved in 250 ml of methanol. 1 g of 10 % activated palladium-on-carbon is added and magnetic stirring is

carried out under a hydrogen atmosphere for 12 hours. The palladiated carbon is then filtered off, and the methanol is evaporated off under reduced pressure. The oil obtained is purified by chromatography on silica gel.

*Step D* : 4-(4-Fluorophenyl)butanoic acid

0.076 mol of the compound obtained in Step C is introduced in a 500 ml round-bottomed flask, and then 250 ml of water and 0.152 mol of NaOH are added. The reaction mixture is stirred for 12 hours at ambient temperature. The reaction mixture is then acidified with 3M HCl and is extracted twice with ethyl ether. The organic phase is dried over $MgSO_4$ and evaporated under reduced pressure to obtain the title product in the form of a white solid.

*Melting point = 38°C*

*Step E* : 7-Fluoro-3,4-dihydro-1(*2H*)-naphthalenone

0.055 mol of the compound obtained in Step D is introduced into a 500 ml round-bottomed flask together with 100 g of polyphosphoric acid. The reaction mixture is heated at 60°C for 4 hours. The mixture is then cooled and poured into water; the precipitate formed is then dried and recrystallised.

*Melting point = 57°C*

*Step F* : 2-[7-Fluoro-3,4-dihydro-1(*2H*)-naphthalenylidene]acetonitrile

1.6 eq. of NaH are suspended in 130 ml of anhydrous THF under a nitrogen atmosphere in a 250 ml three-necked flask. The mixture is cooled in a bath of ice/salt and 1.6 eq. of diethyl cyanomethylenephosphonate in 40 ml of THF are added dropwise. The reaction mixture is stirred for 45 minutes and then, whilst still cold, 1 eq. of the compound obtained in Step E, in 70 ml of THF, is added dropwise. The mixture is stirred for 4 hours and is then poured onto a mixture of ice/water, acidified with 3M HCl solution and extracted 3 times with ethyl ether. The organic phase is dried over $MgSO_4$ and evaporated under reduced pressure; the residue obtained is recrystallised.

*Melting point = 124-125°C*

*Step G* : 2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthyl)-1-ethylamine hydrochloride

0.011 mol of the compound obtained in Step F is dissolved in 100 ml of 95° alcohol and introduced into a 400 ml autoclave; 0.5 g of Raney nickel is then added. The solution is saturated with ammonia gas, and hydrogen is introduced until a pressure of 50 bars is obtained. The reaction mixture is stirred for 5 hours at 60°C and is then cooled, filtered and evaporated under reduced pressure. The oil obtained is dissolved in anhydrous ethyl ether and a solution of ethyl ether saturated with gaseous hydrogen chloride is added dropwise. The precipitate formed is filtered off under suction and recrystallised.

*Melting point = 121-122°C*

*Step H* : N-[2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthyl)ethyl]acetamide

1 eq. of the compound obtained in Step G is dissolved in 4 ml of pyridine and is cooled in an ice bath before adding 3 eq. of acetic anhydride dropwise. The reaction mixture is stirred for 5 hours at ambient temperature and is then poured into 3M HCl solution and extracted with ethyl ether. The organic phase is washed with 10 % potassium carbonate solution and then with water, dried over $MgSO_4$ and evaporated under reduced pressure. The oil obtained is precipitated from a mixture of ethyl ether/petroleum ether (1/2) and the precipitate formed is filtered off under suction and recrystallised.

*Melting point = 58-59°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 71.40 | 7.71 | 5.95 |
| % found | 71.40 | 7.79 | 5.66 |

**Preparation 240 : N-[2-(6-Bromo-2,3-dihydro-*1H*-1-indenyl)ethyl]acetamide**

The procedure is as in Preparation 134.

**Preparation 241** : **N-[2-(6-Iodo-2,3-dihydro-*1H*-1-indenyl)ethyl]acetamide**

The procedure is as in Preparation 160.

**Preparation 242** : **N-[2-(7-Bromo-3-phenyl-1-naphthyl)ethyl]acetamide**

The procedure is as in Preparation 134.

**Preparation 243** : **N-[2-(7-Iodo-3-phenyl-1-naphthyl)ethyl]acetamide**

The procedure is as in Preparation 160.

**Preparation 244** : **N-[2-(7-Iodo-1,2,3,4-tetrahydro-1-naphthyl)ethyl]acetamide**

The procedure is as in Preparation 160.

**Preparation 245** : **N-[2-(5-Bromobenzo[*b*]furan-3-yl)ethyl]acetamide**

The procedure is as in Preparation 134.

**Preparation 246** : **N-[2-(5-Iodobenzo[*b*]furan-3-yl)ethyl]acetamide**

The procedure is as in Preparation 160.

Preparations 247 to 257 are obtained by proceeding as in Preparation 224.

**Preparation 247** : **N-[2-(5-Bromo-1-benzothiophen-3-yl)ethyl]-2-phenylacetamide**

*Melting point = 147-148.2°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 57.76 | 4.31 | 3.74 |
| % found | 57.77 | 4.33 | 3.85 |

**Preparation 248** : **N-[2-(5-Bromo-1-benzothiophen-3-yl)ethyl]-3,4-dichlorobenzamide**

*Melting point = 170-171°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 48.78 | 3.18 | 3.16 |
| % found | 48.88 | 3.20 | 3.38 |

**Preparation 249** : **N-[2-(5-Bromo-1-benzothiophen-3-yl)ethyl]-2-furamide**

*Melting point = 87-88°C*

**Preparation 250** : **N-[2-(5-Chloro-1-benzothiophen-3-yl)ethyl]-2-butynamide**

*Melting point = 79-80°C*

**Preparation 251** : **4-Chloro-N-[2-(5-chloro-1-benzothiophen-3-yl)ethyl]butanamide**

*Melting point = 83-84°C*

**Preparation 252** : **N-[2-(5-Chloro-1-benzothiophen-3-yl)ethyl]-2-furamide**

*Melting point = 70-71°C*

**Preparation 253** : **N-[2-(5-Bromo-2-phenyl-1-benzothiophen-3-yl)ethyl]acetamide**

*Melting point = 140-141°C*

**Preparation 254** : **N-[2-(5-Chloro-1-benzothiophen-3-yl)ethyl]-3-phenyl-2-propenamide**

*Melting point = 162-163°C*

**Preparation 255** : **N-[2-(5-Bromo-1-benzothiophen-3-yl)ethyl]-3-phenyl-2-propenamide**

*Melting point = 152-153°C*

**Preparation 256** : **N-[2-(5-Chloro-1-benzothiophen-3-yl)ethyl]-4-phenyl-3-butenamide**

*Melting point = 116-117°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 67.49 | 5.09 | 3.93 |
| % found | 66.99 | 5.22 | 3.97 |

**Preparation 257 : N-[2-(5-Bromo-1-benzothiophen-3-yl)ethyl]-4-phenyl-3-butenamide**

*Melting point = 130-131°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 60.00 | 4.53 | 3.50 |
| % found | 60.19 | 4.61 | 3.51 |

**Preparation 258 : N-[2-(5-Chloro-1-benzothiophen-3-yl)ethyl]-3-butenamide**

*Melting point = 76-77°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 51.86 | 4.35 | 4.32 |
| % found | 51.86 | 4.30 | 4.16 |

**Preparation 259 : N-[2-(5-Bromo-2-phenyl-1-benzothiophen-3-yl)ethyl]-3-butenamide**

*Melting point = 109-111°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 60.01 | 4.53 | 3.50 |
| % found | 59.97 | 4.48 | 3.24 |

**Preparation 260 : 2-Bromo-N-[2-(5-chloro-1-benzothiophen-3-yl)ethyl]acetamide**

**Preparation 261 : 2-Bromo-N-[2-(5-bromo-1-benzothiophen-3-yl)ethyl]acetamide**

**EXAMPLE 1 : N-{2-[7-(Methylthio)-1-naphthyl]ethyl}acetamide**

At 0°C and with vigorous stirring, potassium carbonate (1.98 mmol) and acetyl chloride (1.82 mmol) are added to a solution of the product obtained in Preparation 1 (1.65 mmol) in a mixture of dichloromethane and water (2/1 ml). The reaction mixture is stirred for 30 minutes and the two phases are then separated. The organic phase is washed with water, dried over magnesium sulphate and evaporated. The residue is purified by chromatography on silica gel (eluant: acetone/toluene/cyclohexane 30/50/20) and is then recrystallised from a mixture of cyclohexane and toluene to yield the title acetamide in the form of a white solid.

*Melting point = 104-106°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 69.49 | 6.60 | 5.40 |
| % found | 69.78 | 6.44 | 5.36 |

**EXAMPLE 2 : N-{2-[7-(Methylthio)-1-naphthyl]ethyl}butanamide**

By proceeding as in Example 1, but replacing the acetyl chloride by butanoyl chloride, the title product is obtained.

*Melting point = 55-57°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 71.04 | 7.36 | 4.87 |
| % found | 70.87 | 7.52 | 5.15 |

**EXAMPLE 3 : N-{2-[7-(Methylthio)-1-naphthyl]ethyl}-1-cyclopropanecarboxamide**

By proceeding as in Example 1, but replacing the acetyl chloride by cyclopropanecarboxylic acid chloride, the title product is obtained in the form of a white solid.

*Melting point = 96-98°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 71.54 | 6.71 | 4.91 |
| % found | 71.34 | 6.56 | 4.95 |

**EXAMPLE 4 : N-{2-[7-(Methylthio)-1-naphthyl]ethyl}-2,2,2-trifluoroacetamide**

At 0°C, pyridine (2.21 mmol) and trifluoroacetic anhydride (1.61 mmol) are added in succession to a solution of the product obtained in Preparation 1 (1.47 mmol) in 5 ml of dichloromethane. Stirring is carried out for 16 hours at ambient temperature and the reaction mixture is then washed with water, dried over magnesium sulphate and evaporated. The residue is chromatographed on silica gel (eluant: petroleum ether/dichloromethane 50/50) and is then recrystallised from a mixture of ethanol and water to yield the title product in the form of a white solid.

*Melting point = 94-96°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 57.50 | 4.50 | 4.47 |
| % found | 57.11 | 4.49 | 4.49 |

**EXAMPLE 5 : N-Methyl-N'-{2-[7-(methylthio)-1-naphthyl]ethyl}urea**

At ambient temperature, methyl isocyanate (2.20 mmol) is added to a solution of the product obtained in Preparation 1 (1.84 mmol) in 8 ml of pyridine. Stirring is carried out for 16 hours at ambient temperature and the reaction mixture is then hydrolysed and subsequently extracted with ethyl acetate. The organic phase is washed with 3N hydrochloric acid solution and then with water, dried over magnesium sulphate and evaporated. The residue is purified by chromatography on silica gel (eluant: acetone/toluene/cyclohexane 40/40/20) and is then recrystallised from toluene to yield the title product in the form of a white solid.

*Melting point = 156-158°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 65.66 | 6.61 | 10.21 |
| % found | 65.61 | 6.49 | 9.92 |

**EXAMPLE 6 : N-{2-[3-Benzoyl-7-(methylthio)-1-naphthyl]ethyl}acetamide**

At 0°C, benzoyl chloride (4.44 mmol) is added dropwise to a suspension of aluminium trichloride (7.40 mmol) in 15 ml of dichloromethane. The reaction mixture is stirred at 0°C for 30 minutes; the compound obtained in Example 1, dissolved in 10 ml of dichloromethane, is then added dropwise and stirring is continued for 16 hours. After hydrolysis, the two phases are separated; the organic phase is washed with water, dried over magnesium sulphate and evaporated. The residue is chromatographed on silica gel (eluant: acetone/toluene/cyclohexane 30/50/20) and is recrystallised from a mixture of cyclohexane and toluene to yield the title product in the form of a white solid.

*Melting point = 126-128°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 72.70 | 5.82 | 3.85 |
| % found | 72.66 | 5.95 | 3.84 |

**EXAMPLE 7 : N-{2-[3-Benzyl-7-(methylthio)-1-naphthyl]ethyl}acetamide**

A solution of the product obtained in Example 6 (2.06 mmol) in trifluoroacetic acid (20.6 mmol) is brought to 0°C and then triethylsilane hydride (6.18 mmol) is added dropwise. Stirring is carried out at ambient temperature for one week and a fourth equivalent of triethylsilane hydride is then added. The reaction mixture is stirred for 24 hours more and is then hydrolysed and extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulphate and evaporated. The residue is chromatographed on silica gel (eluant: acetone/toluene/cyclohexane 30/50/20) and is then recrystallised twice from toluene to yield the title product in the form of a white solid.

*Melting point = 126-128°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 75.61 | 6.63 | 4.01 |
| % found | 75.72 | 6.70 | 4.04 |

**EXAMPLE 8 : N-{2-[7-(Ethylthio)-1-naphthyl]ethyl}acetamide**

The product obtained in Preparation 2 (0.01 mmol), diluted with trifluoromethanesulphonic acid (0.03 mmol), is introduced into a two-necked flask under a nitrogen atmosphere and with stirring. Ethanethiol (0.015 mmol) is added and the mixture is heated at 65°C for 2 hours with the aid of an oil bath. After cooling, the reaction mixture is poured into an ice/water mixture. The aqueous phase is extracted with ethyl acetate, and the organic phases are then washed successively with water, with 10% sodium hydroxide solution and then again with water. After drying over magnesium sulphate and concentrating under reduced pressure, the residue is chromatographed on silica gel (eluant: dichloromethane/ethyl acetate 50/50) to yield the pure title product.

*Melting point = 65-66°C*

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 70.29 | 7.00 | 5.12 |
| % found | 70.21 | 7.04 | 5.10 |

**EXAMPLE 9 : N-{2-[7-(Propylthio)-1-naphthyl]ethyl}acetamide**

By proceeding as in Example 8, but replacing the ethanethiol by propanethiol, the title product is obtained in the form of an oil.

*Elemental microanalysis :*

| | C | H | N |
|---|---|---|---|
| % calculated | 71.04 | 7.36 | 4.87 |
| % found | 71.26 | 7.49 | 4.75 |

**EXAMPLE 10 : N-[2-(7-Mercapto-1-naphthyl)ethyl]benzamide**

The product obtained in Preparation 5 (9 mmol) is added to a solution of potassium hydroxide (10 mmol) dissolved in 15 ml of water and 16 ml of tetrahydrofuran, with stirring. The solution is cooled using a bath of ice and salt, and dimethylthiocarbamoyl chloride (9 mmol) dissolved in tetrahydrofuran (15 ml) is added dropwise, without stirring. After stirring for half an hour, whilst maintaining the cold state, the reaction mixture is extracted with chloroform. The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated under reduced pressure. The residue is taken up in diphenyl ether (10 ml) and is heated at reflux for one hour under a nitrogen atmosphere. The diphenyl ether is evaporated off under reduced pressure until a solution of approximately 2 ml is obtained. The 2 ml of distillate, whilst still hot, are poured with caution into 50 ml of hexane to yield, after cooling, a solid that is isolated by filtration.
The solid thus collected is added to a solution of potassium hydroxide (380 mg) dissolved in a mixture of water/methanol (1 ml/10ml). The solution is heated at reflux for 12 hours and is then cooled and concentrated under reduced pressure. The residue is taken up in 20 ml of chloroform and is extracted 3 times with water. The organic phase is dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue is chromatographed on silica gel to yield the title product.

Examples 11 to 36 are obtained by proceeding as in Example 10, starting from the appropriate hydroxylated compound.

**EXAMPLE 11 : N-[2-(7-Mercapto-1-naphthyl)ethyl]heptanamide**

*Starting compound : Preparation 10*

**EXAMPLE 12 : N-[2-(8-Allyl-7-mercapto-1-naphthyl)ethyl]-N'-cyclobutylthiourea**

*Starting compound : Preparation 16*

**EXAMPLE 13 : N-Cyclohexyl-4-(7-mercapto-1-naphthyl)butanamide**

*Starting compound : Preparation 21*

**EXAMPLE 14 : N-Methyl-N'-propyl-N-[2-(7-mercapto-1-naphthyl)ethyl]urea**

*Starting compound : Preparation 25*

**EXAMPLE 15 : N-Di-(4-chlorophenyl)methyl-N'-[2-(7-mercapto-1-naphthyl)ethyl]urea**

*Starting compound : Preparation 27*

**EXAMPLE 16 : N-[3-(7-Mercapto-1-naphthyl)propyl]-1-cyclohexanecarboxamide**

*Starting compound : Preparation 34*

**EXAMPLE 17 : N-[2-(2-Mercapto-1-naphthyl)ethyl]-2,2,2-trifluoroacetamide**

*Starting compound : Preparation 36*

**EXAMPLE 18 : N-[2-(3-Benzoyl-7-mercapto-1-naphthyl)ethyl]-N'-propylurea**

*Starting compound : Preparation 42*

**EXAMPLE 19 : N-[2-(3-Benzyl-7-mercapto-1-naphthyl)ethyl]-1-cyclohexanecarboxamide**

*Starting compound : Preparation 48*

**EXAMPLE 20 : N-[2-(5-Mercaptobenzo[*b*]furan-3-yl)ethyl]acetamide**

*Starting compound : Preparation 56*

**EXAMPLE 21 : N-[2-(4-Allyl-5-mercaptobenzo[*b*]thiophen-3-yl)ethyl]benzamide**

*Starting compound : Preparation 61*

**EXAMPLE 22 : N-{2-[2-(4-Fluorobenzyl)-1-methyl-5-mercapto-*1H*-pyrrolo[*2,3-b*]-pyridin-3-yl]ethyl}acetamide**

*Starting compound : Preparation 69*

**EXAMPLE 23 : N-[2-(2-Phenyl-5-mercapto-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl)ethyl]-3-butenamide**

*Starting compound : Preparation 73*

**EXAMPLE 24 : N-[2-(2-Benzyl-5-mercaptobenzo[*b*]furan-3-yl)ethyl]-1-cyclopropane-carboxamide**

*Starting compound : Preparation 77*

**EXAMPLE 25 : N-[(6-Mercapto-3,4-dihydro-*2H*-4-chromenyl)methyl]acetamide**

*Starting compound : Preparation 82*

**EXAMPLE 26 : N-Methyl-3-(6-mercapto-*2H*-3-chromenyl)propanamide**

*Starting compound : Preparation 89*

**EXAMPLE 27 : N-[2-(6-Mercapto-3,4-dihydro-*2H*-4-thiochromenyl)ethyl]acetamide**

*Starting compound : Preparation 92*

**EXAMPLE 28 : N-[(3-Benzyl-7-mercapto-1,4-benzodioxin-2-yl)methyl]acetamide**

*Starting compound : Preparation 94*

**EXAMPLE 29 : N-[2-(6-Mercapto-2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]acetamide**

*Starting compound : Preparation 99*

**EXAMPLE 30 : N-[2-(5-Mercaptobenzo[*d*]isoxazol-3-yl)ethyl]-1-cyclopropane-carboxamide**

*Starting compound : Preparation 101*

**EXAMPLE 31 : N-Methyl-9-mercaptobenzo-*3H*-benzo[*f*]chromene-2-carboxamide**

*Starting compound : Preparation 106*

**EXAMPLE 32 : N-Cyclohexyl-N'-(4-mercapto-2,3-dihydro-*1H*-2-phenalenyl)urea**

*Starting compound : Preparation 110*

**EXAMPLE 33 : N-[2-(4-Mercapto-2,3-dihydro-*1H*-1-phenalenyl)ethyl]-1-cyclopropane-carboxamide**

*Starting compound : Preparation 113*

**EXAMPLE 34 : N-{[2-(2-Furylmethyl)-5-mercaptobenzo[*b*]thiophen-3-yl]methyl}-acetamide**

*Starting compound : Preparation 119*

**EXAMPLE 35 : N-{[2-(3-Phenyl-2-propenyl)-5-mercaptobenzo[*b*]thiophen-3-yl]methyl}-1-cyclobutanecarboxamide**

*Starting compound : Preparation 121*

**EXAMPLE 36 : N-{[7-Mercapto-3-(2-thienyl)-1-naphthyl]methyl}butanamide**

*Starting compound : Preparation 125*

In Examples 37 to 170 the procedure is as in Example 8, but the ethanethiol is replaced by the appropriate thiol and the N-[2-(7-hydroxy-1-naphthyl)ethyl]acetamide by the appropriate hydroxylated compound.

(*Note :* When the thiol used is unstable, it is prepared extemporaneously and stored under argon.)

**EXAMPLE 37 : N-{2-[7-(Allylthio)-1-naphthyl]ethyl}-2-phenylacetamide**

*Starting compounds : Preparation 3 and 2-propene-1-thiol*

**EXAMPLE 38 : N-{2-[7-(Cyclohexylthio)-1-naphthyl]ethyl}-2-thiophenecarboxamide**

*Starting compounds : Preparation 7 and cyclohexanethiol*

**EXAMPLE 39 : N-{2-[7-(Benzylthio)-1-naphthyl]ethyl}heptanamide**

*Starting compounds : Preparation 10 and benzylthiol*

**EXAMPLE 40 : N-{2-[7-(2-Propynylthio)-1-naphthyl]ethyl}-2-bromoacetamide**

*Starting compounds : Preparation 8 and 2-propyne-1-thiol*

**EXAMPLE 41 : N-{2-[7-((4-Methylphenyl)thio)-1-naphthyl]ethyl}-3-(trifluoromethyl)-benzamide**

*Starting compounds : Preparation 6 and 4-methylphenylthiol*

**EXAMPLE 42 : Methyl 2-{[8-(2-{[2-(2-oxotetrahydro-*1H*-1-pyrrolyl)acetyl]amino}ethyl)-2-naphthyl]thio}benzoate**

*Starting compounds : Preparation 4 and methyl 2-mercaptobenzoate*

**EXAMPLE 43 : N-{2-[7-((Cyclopropylmethyl)thio)-1-naphthyl]ethyl}-4-chloro-butanamide**

*Starting compounds : Preparation 9 and cyclopropylmethanethiol*

**EXAMPLE 44 : N-{2-[8-Allyl-7-(isopropylthio)-1-naphthyl]ethyl}acetamide**

*Starting compounds : Preparation 11 and isopropanethiol*

**EXAMPLE 45 : N-{2-[8-Allyl-7-(2-pyridylthio)-1-naphthyl]ethyl}heptanamide**

*Starting compounds : Preparation 12 and 2-pyridinethiol*

**EXAMPLE 46 : Methyl 4-{[8-(2-(acetylamino)ethyl)-1-propenyl-2-naphthyl]thio}-butanoate**

*Starting compounds : Preparation 13 and methyl 4-mercaptobutanoate*

**EXAMPLE 47 : N-{2-[7-(2-Butynylthio)-8-(2-propynyl)-1-naphthyl]ethyl}-2-acetamide**

*Starting compounds : Preparation 14 and 2-propynyl-1-thiol*

**EXAMPLE 48 : N-{2-[8-Hexyl-7-(hexylthio)-1-naphthyl]ethyl}-2-phenylacetamide**

*Starting compounds : Preparation 15 and hexanethiol*

**EXAMPLE 49 : N-{2-[8-Allyl-7-(benzylthio)-1-naphthyl]ethyl}-N'-cyclobutylthiourea**

*Starting compounds : Preparation 16 and benzylthiol*

**EXAMPLE 50 : N-{2-[8-Hexyl-7-(cyclohexylthio)-1-naphthyl]ethyl}-2-phenylacetamide**

*Starting compounds : Preparation 15 and cyclohexanethiol*

**EXAMPLE 51 : N-Methyl-2-[7-(cyclopentylthio)-1-naphthyl]acetamide**

*Starting compounds : Preparation 17 and cyclopentanethiol*

**EXAMPLE 52 : N-Cyclobutyl-3-[7-(2-propynylthio)-1-naphthyl]propanamide**

*Starting compounds : Preparation 18 and 2-propynyl-1-thiol*

**EXAMPLE 53 : N-Propyl-4-[7-(benzylthio)-1-naphthyl]butanamide**

*Starting compounds : Preparation 19 and benzylthiol*

**EXAMPLE 54 : N-Cyclopropylmethyl-2-[7-(*1H*-5-imidazolylthio)-1-naphthyl]acetamide**

*Starting compounds : Preparation 20 and 1H-5-imidazolylthiol*

**EXAMPLE 55 : N-Cyclohexyl-4-[7-(phenylthio)-1-naphthyl]butanamide**

*Starting compounds : Preparation 21 and benzenethiol*

**EXAMPLE 56 : N-Allyl-3-[7-(neopentylthio)-1-naphthyl]propanamide**

*Starting compounds : Preparation 22 and neopentylthiol*

**EXAMPLE 57 : N-Cyclobutyl-N'-{2-[7-(2-propynylthio)-1-naphthyl]ethyl}urea**

*Starting compounds : Preparation 23 and 2-propynyl-1-thiol*

**EXAMPLE 58 : N-Isopropyl-N'-{2-[7-((4-(trifluoromethyl)benzyl)thio)-1-naphthyl]ethyl}-urea**

*Starting compounds : Preparation 24 and 4-trifluoromethylbenzylthiol*

**EXAMPLE 59 : N-{2-[7-(*tert*-Butylthio)-1-naphthyl]ethyl}-N-methyl-N'-propylurea**

*Starting compounds : Preparation 25 and tert-butylthiol*

**EXAMPLE 60 : Methyl 2-{[8-(2-[((butylamino)carbothioyl)amino]ethyl)-2-naphthyl]-thio}benzoate**

*Starting compounds : Preparation 26 and methyl 2-mercaptobenzoate*

**EXAMPLE 61 : N-Di-(4-chlorophenyl)methyl-N'-{2-[7-(2-pyridylthio)-1-naphthyl]ethyl}-urea**

*Starting compounds : Preparation 27 and 2-pyridinethiol*

**EXAMPLE 62 : N-{2-[7-(Cyclopentylthio)-1-naphthyl]ethyl}-N-methyl-N'-propylurea**

*Starting compounds : Preparation 25 and cyclopentanethiol*

**EXAMPLE 63 : Methyl 4-{[8-(2-methoxy-1-{[(2-morpholinoacetyl)amino]methyl}-2-oxoethyl))-2-naphthyl]thio}butanoate**

*Starting compounds : Preparation 28 and methyl 4-mercaptobutanoate*

**EXAMPLE 64 : Methyl 3-[(cyclopropylcarbonyl)amino]-2-[7-(2-propynylthio)-1-naphthyl]propanoate**

*Starting compounds : Preparation 29 and 2-propynethiol*

**EXAMPLE 65 : Methyl 2-[7-(phenylthio)-1-naphthyl]-3-[(2,2,2-trifluoroacetyl)amino]-propanoate**

*Starting compounds : Preparation 30 and benzenethiol*

**EXAMPLE 66 : Methyl 2-{[7-(cyclopropylmethyl)thio]-1-naphthyl}-3-[(2,2,2-trifluoro-acetyl)amino]propanoate**

*Starting compounds : Preparation 30 and cyclopropylmethylthiol*

**EXAMPLE 67 : O-{2[7-(2-Propynylthio)-1-naphthyl]methyl}-N-acetyl-hydroxylamine**

*Starting compounds : Preparation 31 and 2-propynethiol*

**EXAMPLE 68 : O-{[7-(Phenylthio)-1-naphthyl]methyl}-N-(2-butenoyl)hydroxylamine**

*Starting compounds : Preparation 32 and benzenethiol*

**EXAMPLE 69 : O-{[7-(Cyclohexylmethylthio)-1-naphthyl]methyl}-N-acetylhydroxyl-amine**

*Starting compounds : Preparation 31 and cyclohexylmethanethiol*

**EXAMPLE 70 : N-{3-[7-(1-Propenylthio)-1-naphthyl]propyl}acetamide**

*Starting compounds : Preparation 33 and 1-propenethiol*

**EXAMPLE 71 : N-{3-[7-(Butylthio)-1-naphthyl]propyl}-1-cyclohexanecarboxamide**

*Starting compounds : Preparation 34 and butanethiol*

**EXAMPLE 72 : N-{3-[7-(Benzylthio)-1-naphthyl]propyl}-N'-propylthiourea**

*Starting compounds : Preparation 35 and benzylthiol*

**EXAMPLE 73 : N-{3-[7-([1-Isopropyl-2-propynyl]thio)-1-naphthyl]propyl}acetamide**

*Starting compounds : Preparation 33 and 1-isopropyl-2-propynylthiol*

**EXAMPLE 74 : N-{2-[2(Phenylthio)-1-naphthyl]ethyl}-2,2,2-trifluoroacetamide**

*Starting compounds : Preparation 36 and benzenethiol*

**EXAMPLE 75 : N-{2-[2-(2-Pyridylthio)-1-naphthyl]ethyl}-2-butenamide**

*Starting compounds : Preparation 37 and 2-pyridinethiol*

**EXAMPLE 76 : N-{2-[2-(2-Cyclohexenylthio)-1-naphthyl]ethyl}-1-cyclohexane-carboxamide**

*Starting compounds : Preparation 38 and 2-cyclohexenylthiol*

**EXAMPLE 77 : N-{1-Methyl-2-[2-(propylthio)-1-naphthyl]ethyl}propanamide**

*Starting compounds : Preparation 39 and propanethiol*

**EXAMPLE 78 : N-{2-[7-(Allylthio)-3-phenyl-1-naphthyl]ethyl}acetamide**

*Starting compounds : Preparation 40 and 2-propenethiol*

**EXAMPLE 79 : N-{2-[7-(Benzylthio)-3-phenyl-1-naphthyl]ethyl}acetamide**

*Starting compounds : Preparation 40 and benzylthiol*

**EXAMPLE 80 : Methyl 2-{[8-(2-[acetylamino]ethyl)-6-benzoyl-2-naphthyl]thio}benzoate**

*Starting compounds : Preparation 41 and methyl 2-mercaptobenzoate*

**EXAMPLE 81 : N-{2-[3-Benzoyl-7-(2-propynylthio)-1-naphthyl]ethyl}-N'-propylurea**

*Starting compounds : Preparation 42 and 2-propynylthiol*

**EXAMPLE 82 : N-{2-[3-(Cyclopropylcarbonyl)-7-(isopropylthio)-1-naphthyl]ethyl}-1-cyclobutanecarboxamide**

*Starting compounds : Preparation 43 and isopropanethiol*

**EXAMPLE 83 : N-{2-[7-(Cyclopentylthio)-3-(cyclopropylcarbonyl)-1-naphthyl]ethyl}-N'-propylurea**

*Starting compounds : Preparation 44 and cyclopentanethiol*

**EXAMPLE 84 : N-{2-[3,7-Di-(1-propenylthio)-1-naphthyl]ethyl}propanamide**

*Starting compounds : Preparation 45 and 1-propenethiol*

***Note :*** *The procedure is as in the preceding Examples, but twice the equivalents of the thiol are used.*

**EXAMPLE 85 : Methyl 4-{[6-(acetyloxy)-8-(2-[(cyclopropylcarbonyl)amino]ethyl)-2-naphthyl]thio}butanoate**

*Starting compounds : Preparation 46 and methyl 4-mercaptobutanoate*

**EXAMPLE 86 : N-{2-[(3-Benzyl-7-[(2,5-dihydro-*1H*-4-imidazolylthio]ethyl)-1-naphthyl]-ethyl}pentanamide**

*Starting compounds : Preparation 47 and 2,5-dihydro-1H-4-imidazolethiol*

**EXAMPLE 87 : N-{2-[3-Benzyl-7-(benzylthio)-1-naphthyl]ethyl}-N'-cyclohexylurea**

*Starting compounds : Preparation 48 and benzylthiol*

**EXAMPLE 88 : N-Cyclohexyl-N'-{2-[3-ethyl-7-(isobutylthio)-1-naphthyl]ethyl}urea**

*Starting compounds : Preparation 49 and isobutanethiol*

**EXAMPLE 89 : N-{2[3-(Cyclopropylmethyl)-7-(hexylthio)-1-naphthyl]ethyl}acetamide**

*Starting compounds : Preparation 50 and hexanethiol*

**EXAMPLE 90 : N-{[5-(Phenylthio)benzofuran-3-yl]methyloxy}-N'-propylthiourea**

*Starting compounds : Preparation 51 and benzenethiol*

**EXAMPLE 91 : N-{3-[5-([1-Methyl-2-propynyl]thio)benzo[*b*]furan-3-yl]propyl}-acetamide**

*Starting compounds : Preparation 52 and 1-methyl-2-propynethiol*

**EXAMPLE 92 : N-[2-(2-Methyl-5-{[4-(trifluoromethyl)benzyl]thio}benzo[*b*]furan-3-yl)-ethyl]heptanamide**

*Starting compounds : Preparation 53 and 4-trifluoromethylbenzenethiol*

**EXAMPLE 93 : N-Methyl-4-[5-(cyclohexylthio)benzo[*b*]furan-3-yl]butanamide**

*Starting compounds : Preparation 54 and cyclohexanethiol*

**EXAMPLE 94 : N-{2-(4-Allyl-[5-[(3-phenyl-2-propenyl)thio]benzo[*b*]furan-3-yl]ethyl}-benzamide**

*Starting compounds : Preparation 55 and 3-phenyl-2-propanethiol*

**EXAMPLE 95 : N-{2-[5-(2-Pyridylthio)benzo[*b*]furan-3-yl]ethyl}acetamide**

*Starting compounds : Preparation 56 and 2-pyridinethiol*

**EXAMPLE 96 : O-{[5-([1-(*tert*-Butyl)-2-propynyl]thio)benzothiophen-3-yl]methyl}-N-thiopropionylhydroxylamine**

*Starting compounds : Preparation 57 and 1-tert-butyl-2-propynethiol*

**EXAMPLE 97 : N-{3-[5-(Benzylthio)benzo[*b*]thiophen-3-yl]propyl}-1-cyclopropane-carboxamide**

*Starting compounds : Preparation 58 and benzylthiol*

**EXAMPLE 98 : N-{[2-Benzyl-5-(3-butenylthio)benzo[*b*]thiophen-3-yl]methyl}acetamide**

*Starting compounds : Preparation 59 and 3-butenethiol*

**EXAMPLE 99 : Methyl 2{[3-(acetylamino]methyl)thieno[*3,2-b*]pyridin-5-yl]thio} benzoate**

*Starting compounds : Preparation 60 and methyl 2-mercaptobenzoate*

**EXAMPLE 100 : N-{2-[4-Allyl-5-(allylthio)benzo[*b*]thiophen-3-yl]ethyl}benzamide**

*Starting compounds : Preparation 61 and 2-propene-1-thiol*

**EXAMPLE 101 : N-{2-[5-({3-Phenyl-2-propenyl}thio)-*1H*-4-indolyl]ethyl}-1-cyclopropane-carboxamide**

*Starting compounds : Preparation 62 and 3-phenyl-2-propenethiol*

**EXAMPLE 102 : N-Methyl-4-[5-(2-propynylthio)-*1H*-3-indolyl]butanamide**

*Starting compounds : Preparation 63 and 2-propynethiol*

**EXAMPLE 103 : N-{2-[5-(2-Pyridylthio)-*1H*-3-indolyl]ethyl}-2-morpholinoacetamide**

*Starting compounds : Preparation 64 and 2-pyridinethiol*

**EXAMPLE 104 : N-Benzyl-N'-{2-[5-(*tert*-butylthio)-*1H*-3-indolyl]ethyl}urea**

*Starting compounds : Preparation 65 and tert-butylthiol*

**EXAMPLE 105 : N-{2-[5-([Cyclopentylmethyl]thio)-*1H*-3-indolyl]ethyl}benzamide**

*Starting compounds : Preparation 66 and cyclopentylmethanethiol*

**EXAMPLE 106 : N-{2-[1-Methyl-2-phenyl-5-(propylthio)-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl]-ethyl}acetamide**

*Starting compounds : Preparation 67 and propanethiol*

**EXAMPLE 107 : N-{2-[2-(2-Methoxyphenyl)-1-methyl-5-(2-propynylthio)-*1H*-pyrrolo-[*2,3-b*]pyridin-3-yl]ethyl}acetamide**

*Starting compounds : Preparation 68 and 2-propynethiol*

**EXAMPLE 108 : N-{2-[2-(4-Fluorobenzyl)-1-methyl-5-{[4-(trifluoromethyl)benzyl]thio}-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl]ethyl}acetamide**

*Starting compounds : Preparation 69 and 4-trifluoromethylbenzylthiol*

**EXAMPLE 109 : N-[2-(2-Benzyl-1-methyl-5-[(3-phenyl-2-propenyl)thio]-*1H*-pyrrolo-[*2,3-b*]pyridin-3-yl)ethyl]acetamide**

*Starting compounds : Preparation 70 and 3-phenyl-2-propenethiol*

**EXAMPLE 110 : N-{2-[5-(2-Pyridylthio)-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl]ethyl}acetamide**

*Starting compounds : Preparation 71 and 2-pyridinethiol*

**EXAMPLE 111 : N-{2-[5-(1-Propenylthio)-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl]ethyl}-2,2,2-trifluoroacetamide**

*Starting compounds : Preparation 72 and 1-propenethiol*

**EXAMPLE 112 : N-{2-[5-([1-Cyclohexyl-2-propynyl]thio)-2-phenyl-*1H*-pyrrolo[*2,3-b*]-pyridin-3-yl]ethyl}acetamide**

*Starting compounds : Preparation 73 and 1-cyclohexyl-2-propynethiol*

**EXAMPLE 113 : N-{2-[5-(2-Cyclohexenylthio)-2-phenyl-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl]-ethyl}acetamide**

*Starting compounds : Preparation 73 and 2-cyclohexenethiol*

**EXAMPLE 114 : Methyl 2-{[3-(2-[(cyclobutylcarbonyl)amino]ethyl)-*1H*-pyrrolo[*2,3-b*]-pyridin-5-yl]thio}benzoate**

*Starting compounds : Preparation 75 and methyl 2-mercaptobenzoate*

**EXAMPLE 115 : N-{2-[5-(Benzylthio)-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl]ethyl}-N'-butyl-thiourea**

*Starting compounds : Preparation 76 and benzylthiol*

**EXAMPLE 116 : N-{2-[5-(Allylthio)-2-benzylbenzo[*b*]furan-3-yl]ethyl}-1-cyclopropane-carboxamide**

*Starting compounds : Preparation 77 and 2-propenethiol*

**EXAMPLE 117 : N-{2-[5-(*tert*-Butylthio)-2-benzylbenzo[*b*]furan-3-yl]ethyl}-1-cyclopropanecarboxamide**

*Starting compounds : Preparation 77 and tert-butylthiol*

**EXAMPLE 118 : N-{2-[6-(2-Cyclohexenylthio)-*1H*-benzo[*d*]imidazol-1-yl]ethyl}-1-cyclopropanecarboxamide**

*Starting compounds : Preparation 78 and 2-cyclohexenethiol*

**EXAMPLE 119 : N-{2-[5-(3-Butynylthio)-2-benzylbenzo[*b*]furan-3-yl]ethyl}-1-cyclopropanecarboxamide**

*Starting compounds : Preparation 77 and 3-butynylthiol*

**EXAMPLE 120 : N-{2-[5-(Propylthio)-2-phenylbenzo[*b*]thiophen-3-yl]ethyl}acetamide**

*Starting compounds : Preparation 210 and propylthiol*

**EXAMPLE 121 : N-{[6-([1-Methyl-*1H*-2-imidazolyl]thio)-3,4-dihydro-*2H*-3-yl-chromenyl]-methyl}acetamide**

*Starting compounds : Preparation 79 and 1-methyl-1H-2-imidazolylthiol*

**EXAMPLE 122 : N-{[6-(Allylthio)-3,4-dihydro-*2H*-3-chromenyl]methyl}-1-cyclopropane-carboxamide**

*Starting compounds : Preparation 80 and 2-propenethiol*

**EXAMPLE 123 : N-{2-[5-(2-Cyclohexenylthio)benzo[*b*]thiophen-3-yl]ethyl}acetamide**

*Starting compounds : Preparation 211 and 2-cyclohexenethiol*

**EXAMPLE 124 : N-{[6-(Benzylthio)-3,4-dihydro-*2H*-4-chromenyl]methyl}acetamide**

*Starting compounds : Preparation 82 and benzylthiol*

**EXAMPLE 125 : Methyl 2-{[4-([butyrylamino]methyl)-3,4-dihydro-*2H*-6-chromenyl]thio}-benzoate**

*Starting compounds : Preparation 83 and methyl 2-mercaptobenzoate*

**EXAMPLE 126 : N-{2-[6-([(4-Trifluoromethyl)benzyl]thio)-3,4-dihydro-*2H*-4-chromenyl]-ethyl}-3-butenamide**

*Starting compounds : Preparation 84 and 4-trifluoromethylbenzylthiol*

**EXAMPLE 127 : N-{2-[6-(2-Propynylthio)-3,4-dihydro-*2H*-4-chromenyl]ethyl}acetamide**

*Starting compounds : Preparation 85 and 2-propynethiol*

**EXAMPLE 128 : N-{2-[6-([Cyclopropylmethyl]thio)-3,4-dihydro-*2H*-4-chromenyl]ethyl}-2-phenylacetamide**

*Starting compounds : Preparation 86 and cyclopropylmethanethiol*

**EXAMPLE 129 : N-{[6-(Cyclobutylthio)-*2H*-3-chromenyl]methyl}acetamide**

*Starting compounds : Preparation 87 and 2-cyclobutanethiol*

**EXAMPLE 130 : N-{[6-(Allylthio)-*2H*-3-chromenyl]methyl}butanamide**

*Starting compounds : Preparation 88 and 2-propenethiol*

**EXAMPLE 131 : N-Methyl-3-{6-[(1-isopropyl-2-propynyl)thio]-*2H*-3-chromenyl}-propanamide**

*Starting compounds : Preparation 89 and 1-isopropyl-2-propynethiol*

**EXAMPLE 132 : N-{[6-(Benzylthio)-2-phenyl-*2H*-3-chromenyl]methyl}acetamide**

*Starting compounds : Preparation 90 and benzylthiol*

**EXAMPLE 133 : N-{[2-Phenyl-6-(2-pyridylthio)-*2H*-3-chromenyl]methyl}butanamide**

*Starting compounds : Preparation 91 and 2-pyridinethiol*

**EXAMPLE 134 : Methyl 2-{[4-(2-(acetylamino)ethyl)-3,4-dihydro-*2H*-6-thiochromenyl]-thio}benzoate**

*Starting compounds : Preparation 92 and methyl 2-mercaptobenzoate*

**EXAMPLE 135 : N-{[3-Phenyl-7-[(3-phenyl-2-propenyl)thio]-1,4-benzodioxin-2-yl]-methyl}acetamide**

*Starting compounds : Preparation 93 and 3-phenyl-2-propenethiol*

**EXAMPLE 136 : N-{[3-Benzyl-7-(2-propenylthio)-1,4-benzodioxin-2-yl]methyl}acetamide**

*Starting compounds : Preparation 94 and 2-propenethiol*

**EXAMPLE 137 : N-{[7-(2-Cyclohexenylthio)-1,4-benzodioxin-2-yl]methyl}-1-cyclopropanecarboxamide**

*Starting compounds : Preparation 95 and 2-cyclohexenethiol*

**EXAMPLE 138 : N-{2-[5-(Isopentylthio)benzo[*b*]thiophen-3-yl]ethyl}acrylamide**

*Starting compounds : Preparation 212 and isopentanethiol*

**EXAMPLE 139 : N-{2-[7-(2-Propynylthio)-2,3-dihydro-1,4-benzodioxin-2-yl]ethyl}-acetamide**

*Starting compounds : Preparation 97 and 2-propynethiol*

**EXAMPLE 140 : Methyl 4-{[3-(2-anilino-2-oxoethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-thio}butanoate**

*Starting compounds : Preparation 98 and methyl 4-mercaptobutanoate*

**EXAMPLE 141 : N-{2-[7-(2-Pyridylthio)-2,3-dihydro-1,4-benzodioxin-2-yl]ethyl}-acetamide**

*Starting compounds : Preparation 97 and 2-pyridinethiol*

**EXAMPLE 142 : N-{[6-(Cyclopentylthio)-2,3-dihydro-1,4-benzodioxin-5-yl]methyl}-acetamide**

*Starting compounds : Preparation 99 and cyclopentanethiol*

**EXAMPLE 143 : N-{3-[7-(1-Propenylthio)-1,2,3,4-tetrahydro-1-naphthyl]propyl}-acetamide**

*Starting compounds : Preparation 100 and 1-propenethiol*

**EXAMPLE 144 : N-[8-(Ethylthio)-5-methyl-1,2,3,4-tetrahydro-2-naphthyl]acetamide**

*Starting compounds : Preparation 220 and ethanethiol*

**EXAMPLE 145 : N-{2-[5-(Cyclobutylthio)-benzo[*d*]isoxazol-3-yl]ethyl}-1-cyclopropane-carboxamide**

*Starting compounds : Preparation 101 and cyclobutanethiol*

**EXAMPLE 146 : N-{2-[7-((4-Methylphenyl)thio)-1,2,3,4-tetrahydro-1-naphthyl]ethyl}-acetamide**

*Starting compounds : Preparation 219 and 4-methyl-benzenethiol*

**EXAMPLE 147 : N-[9-(Allylthio)-2,3,6,10b-tetrahydro-*1H*-benzo[*f*]chromen-2-yl]-acetamide**

*Starting compounds : Preparation 102 and 2-propenethiol*

**EXAMPLE 148 : N-[9-(Isobutylthio)-2,3,6,10b-tetrahydro-*1H*-benzo[*f*]chromen-2-yl]-2-cyclopropylacetamide**

*Starting compounds : Preparation 103 and isobutanethiol*

**EXAMPLE 149 : N-[9-(Phenylthio)-2,3,6,10b-tetrahydro-*1H*-benzo[*f*]chromen-1-yl]-butanamide**

*Starting compounds : Preparation 104 and benzenethiol*

**EXAMPLE 150 : N-{[9-(Benzylthio)-2,3,6,10b-tetrahydro-*1H*-benzo[*f*]chromen-1-yl]-methyl}acetamide**

*Starting compounds : Preparation 105 and benzylthiol*

**EXAMPLE 151 : Methyl 2-{[2-([methylamino]carbonyl)-6,10b-dihydro-*3H*-benzo[f]chromen-9-yl]thio}benzoate**

*Starting compounds : Preparation 106 and methyl 2-mercaptobenzoate*

**EXAMPLE 152 : N-[4-(Butylthio)-2,3-dihydro-*1H*-2-phenalenyl]propanamide**

*Starting compounds : Preparation 107 and butanethiol*

**EXAMPLE 153 : N-{4-[(1-Methyl-*1H*-2-imidazolyl)thio]-2,3-dihydro-*1H*-2-phenalenyl}-2-methylpropanamide**

*Starting compounds : Preparation 108 and 1-methyl-1H-2-imidazolethiol*

**EXAMPLE 154 : N-Cyclopropyl-N'-[4-(phenylthio)-2,3-dihydro-*1H*-2-phenalenyl]thiourea**

*Starting compounds : Preparation 109 and benzenethiol*

**EXAMPLE 155 : N-Cyclohexyl-N'-{4-[(4-[trifluoromethyl]phenyl)thio]-2,3-dihydro-*1H*-2-phenalenyl}urea**

*Starting compounds : Preparation 110 and 4-trifluoromethylbenzenethiol*

**EXAMPLE 156 : N-[4,9-Di(*tert*-butylthio)-2,3-dihydro-*1H*-2-phenalenyl]acetamide**

*Starting compounds : Preparation 111 and tert-butylthiol*

**EXAMPLE 157 : N-{[4-(Benzylthio)-2,3-dihydro-*1H*-1-phenalenyl]methyl}acetamide**

*Starting compounds : Preparation 112 and benzylthiol*

**EXAMPLE 158 : Methyl 2-{[1-(2-[(cyclopropylcarbonyl)amino]ethyl)-2,3-dihydro-*1H*-4-phenalenyl]thio}benzoate**

*Starting compounds : Preparation 113 and methyl 2-mercaptobenzoate*

**EXAMPLE 159 : N-Methyl-N'-{[4,9-di-([3-phenyl-2-propenyl]thio)-2,3-dihydro-*1H*-1-phenalenyl]methyl}urea**

*Starting compounds : Preparation 114 and 3-phenyl-2-propenethiol*

***Note :*** *The procedure is as in Example 84.*

**EXAMPLE 160 : N-[6-(Cyclopropylthio)-1,3,4,5-tetrahydrobenzo[*cd*]indol-4-yl]acetamide**

*Starting compounds : Preparation 115 and cyclopropanethiol*

**EXAMPLE 161 : N-[6-(2-Cyclohexenylthio)-4,5-dihydro-*3H*-benzo[*cd*]isobenzofuran-4-yl]-acetamide**

*Starting compounds : Preparation 116 and 2-cyclohexenethiol*

**EXAMPLE 162 : N-[6-(Benzylthio)-4,5-dihydro-*3H*-naphtho[*1,8-bc*]thiophen-4-yl]-acetamide**

*Starting compounds : Preparation 117 and benzylthiol*

**EXAMPLE 163 : N-Cyclobutyl-6-(2-pyridylthio)-4,5-dihydro-*3H*-benzo[*cd*]isobenzofuran-4-carboxamide**

*Starting compounds : Preparation 118 and 2-pyridinethiol*

**EXAMPLE 164 : N-{[2-(2-Furylmethyl)-5-(2-propynylthio)benzo[*b*]furan-3-yl]methyl}-acetamide**

*Starting compounds : Preparation 119 and 2-propynethiol*

**EXAMPLE 165 : N-{[5-([Cyclobutylmethyl]thio)-2(3-pyridylmethyl)benzo-[*b*]furan-3-yl]-methyl}benzamide**

*Starting compounds : Preparation 120 and cyclobutylmethanethiol*

**EXAMPLE 166 : N-{[5-(2-Cyclohexenylthio)-2-(3-phenyl-2-propenyl)benzo[*b*]thiophen-3-yl]methyl}-1-cyclobutanecarboxamide**

*Starting compounds : Preparation 121 and 2-cyclohexenethiol*

**EXAMPLE 167 : N-{2-[7-(2-Butenylthio)-3-(2-naphthyl)-1-naphthyl]ethyl}heptanamide**

*Starting compounds : Preparation 122 and 2-butenethiol*

**EXAMPLE 168 : 4-[2-(Benzoylamino)ethyl]-6-(*tert*-butylthio)-2-naphthyl trifluoromethanesulphonate**

*Starting compounds : Preparation 123 and tert-butanethiol*

**EXAMPLE 169 : N-{2-[3-(3-Phenyl-2-propenyl)-7-(2-pyridylthio-1-naphthyl]ethyl}-2-cyclohexylacetamide**

*Starting compounds : Preparation 124 and 2-pyridinethiol*

**EXAMPLE 170 : N-{[7-([4-Isopropylphenyl]thio)-3-(2-thienyl)-1-naphthyl]methyl}-butanamide**

*Starting compounds : Preparation 125 and 4-isopropylphenylthiol*

**EXAMPLE 171 : N-{2-[7-([Cyclopropylmethyl]sulphinyl)-1-naphthyl]ethyl}-4-chlorobutanamide**

The product obtained in Example 43 (10 mmol) is added to an aqueous 0.5M sodium periodate solution (21 ml, 10.5 mmol) at 0°C. Stirring at 0-5°C is carried out overnight. The solution is filtered and the filtrate is extracted with chloroform.

The organic phase is dried over magnesium sulphate and is concentrated under reduced pressure. The residue is chromatographed on silica gel to yield the title compound.

In Examples 172 to 184 the procedure is the same as in Example 171, starting from the appropriate thioether.

**EXAMPLE 172 : N-{2-[7-(Cyclohexylsulphinyl)-8-hexyl-1-naphthyl]ethyl}-2-phenylacetamide**

*Starting compound : Example 50*

**EXAMPLE 173 : N-Cyclopropylmethyl-2-[7-(*1H*-5-imidazolylsulphinyl)-1-naphthyl]-acetamide**

*Starting compound : Example 54*

**EXAMPLE 174 : N-{1-Methyl-2-[2-(propylsulphinyl)-1-naphthyl]ethyl}propanamide**

*Starting compound : Example 77*

**EXAMPLE 175 : N-{2-[3-(Cyclopropylcarbonyl)-7-(isopropylsulphinyl)-1-naphthyl] ethyl}-1-cyclobutanecarboxamide**

*Starting compound : Example 82*

**EXAMPLE 176 : N-{2-[2-Methyl-5-([4-(trifluoromethyl)benzyl]sulphinyl)benzo[*b*]furan-3-yl]ethyl}heptamide**

*Starting compound : Example 92*

**EXAMPLE 177 : N-{3-[5-(Benzylsulphinyl)benzo[*b*]thiophen-3-yl]propyl}-1-cyclopropane-carboxamide**

*Starting compound : Example 97*

**EXAMPLE 178 : N-{2-[5-([Cyclopentylmethyl]sulphinyl)-*1H*-3-indolyl]ethyl}benzamide**

*Starting compound : Example 105*

**EXAMPLE 179 : N-{2-[5-(2-Pyridylsulphinyl)-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl]ethyl}-acetamide**

*Starting compound : Example 110*

**EXAMPLE 180 : N-{2-[2-Benzyl-5-(*tert*-butylsulphinyl)benzo[*b*]furan-3-yl]ethyl}-1-cyclopropanecarboxamide**

*Starting compound : Example 117*

**EXAMPLE 181 : N-{[6-(Benzylsulphinyl)-3,4-dihydro-*2H*-4-chromenyl]methyl}acetamide**

*Starting compound : Example 124*

**EXAMPLE 182 : N-{2-[5-(Cyclobutylsulphinyl)benzo[*d*]isoxazol-3-yl]ethyl}-1-cyclopropanecarboxamide**

*Starting compound : Example 145*

**EXAMPLE 183 : N-[4,9-Di-(*tert*-butylsulphinyl)-2,3-dihydro-*1H*-2-phenalenyl]acetamide**

*Starting compound : Example 156*

**EXAMPLE 184 : N-{[5-(Cyclobutylmethyl)sulphinyl-2-(2-furylmethyl)benzo[*b*]furan-3-yl]-methyl}benzamide**

*Starting compound : Example 165*

**EXAMPLE 185 : N-{2-[7-(Benzylsulphonyl)-1-naphthyl]ethyl}heptanamide**

The product obtained in Example 39 (10 mmol) is dissolved in 40 ml of methanol and is cooled to 0°C with the aid of an ice bath. A 49.5% solution of $KHSO_5$ (30 mmol) in water (40 ml) is added. Stirring is carried out for 4 hours at ambient temperature. The reaction mixture is then diluted with water and extracted 3 times with chloroform. The organic phases are combined, washed with water and with saturated NaCl solution and then dried over $Na_2SO_4$ and concentrated under reduced pressure. The title product is obtained after chromatography on silica gel.

Examples 186 to 193 are obtained by proceeding as in Example 185, starting from the corresponding thioether.

**EXAMPLE 186 : N-Cyclohexyl-4-[7-(phenylsulphonyl)-1-naphthyl]butanamide**

*Starting compound : Example 55*

**EXAMPLE 187 : N-{1-Methyl-2-[2-(propylsulphonyl)-1-naphthyl]ethyl}propanamide**

*Starting compound : Example 77*

**EXAMPLE 188 : N-Methyl-4-[5-(cyclohexylsulphonyl)benzo[*b*]furan-3-yl]butanamide**

*Starting compound : Example 93*

**EXAMPLE 189 : N-{2-[1-Methyl-2-phenyl-5-(propylsulphonyl)-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl]ethyl}acetamide**

*Starting compound : Example 106*

**EXAMPLE 190 : N-{2-[6-([Cyclopropylmethyl]sulphonyl)-3,4-dihydro-*2H*-4-chromenyl]-ethyl}-2-phenylacetamide**

*Starting compound : Example 128*

**EXAMPLE 191 : N-{[6-(Cyclopentylsulphonyl)-2,3-dihydro-1,4-benzodioxin-5-yl]methyl}-acetamide**

*Starting compound : Example 142*

**EXAMPLE 192 : N-[4-(Butylsulphonyl)-2,3-dihydro-*1H*-2-phenalenyl]propanamide**

*Starting compound : Example 152*

**EXAMPLE 193 : N-Cyclobutyl-6-(2-pyridylsulphonyl)-4,5-dihydro-*3H*-benzo[*cd*]-isobenzofuran-4-carboxamide**

*Starting compound : Example 163*

**EXAMPLE 194 : 8-[2-(Benzoylamino)ethyl]-2-naphthyl propanethioate**

Polyphosphate ester (20 ml) is added to a mixture of propanoic acid (30 mmol) and the product obtained in Example 10 (31 mmol) and the reaction mixture is stirred for 15 hours at ambient

temperature. The mixture is then treated with saturated aqueous sodium hydrogen carbonate solution (200 ml) and is extracted with chloroform (3 x 30 ml). The organic phases are combined, dried over magnesium sulphate and then concentrated under reduced pressure. The residue is chromatographed on silica gel to yield the title product.

(Polyphosphate ester is prepared according to the method described by W. Pollmann *et al.*, Biochem. Biophys. Acta, 80 (1), 1964).

Examples 195 to 204 are prepared according to the procedure of Example 194, starting from appropriate reactants.

**EXAMPLE 195 : 1-Allyl-8-{2-[([cyclobutylamino]carbothioyl)amino]ethyl}-2-naphthyl benzenecarbothioate**

*Starting compound : Example 12*

**EXAMPLE 196 : 3-[2-(Acetylamino)ethyl]-2-phenyl-*1H*-pyrrolo[*2,3-b*]pyridin-5-yl cyclopentanecarbothioate**

*Starting compound : Example 23*

**EXAMPLE 197 : 1-{2-[(2,2,2-Trifluoroacetyl)amino]ethyl}-2-naphthyl 2-pentenethioate**

*Starting compound : Example 17*

**EXAMPLE 198 : 6-Benzoyl-8-{2-[([propylamino]carbonyl)amino]ethyl}-2-naphthyl 4-(trifluoromethyl)-1-benzenecarbothioate**

*Starting compound : Example 18*

**EXAMPLE 199 : 4-Allyl-3-[2-(benzoylamino)ethyl]benzo[*b*]thiophen-5-yl 2-cyclobutyl-ethanethioate**

*Starting compound : Example 21*

**EXAMPLE 200 : 2-Benzyl-3-{2-[(cyclopropylcarbonyl)amino]ethyl}benzo[*b*]furan-5-yl 2-(2-oxotetrahydro-*1H*-1-pyrrolyl)ethanethioate**

*Starting compound : Example 24*

**EXAMPLE 201 : 3-[3-(Methylamino)-3-oxopropyl]-*2H*-6-chromenyl 2-morpholino-ethanethioate**

*Starting compound : Example 26*

**EXAMPLE 202 : 3-[(Acetylamino)methyl]-2-benzyl-1,4-benzodioxin-6-yl 2-furan-carbothioate**

*Starting compound : Example 28*

**EXAMPLE 203 : 1-{2-[(Cyclopropylcarbonyl)amino]ethyl}-2,3-dihydro-*1H*-4-phenalenyl ethanethioate**

*Starting compound : Example 33*

**EXAMPLE 204 : 8-[(Butanoylamino)methyl]-6-(2-thienyl)-2-naphthyl 2-butenethioate**

*Starting compound : Example 36*

**EXAMPLE 205 : 8-[(Heptanoylamino)methyl]-2-naphthyl (propylamino)methanethioate**

Propyl isocyanate (11 mmol) and the product obtained in Example 11 (10 mmol) are dissolved in dimethylformamide (20 ml). The reaction mixture is stirred at ambient temperature for 16 hours under nitrogen. After evaporating off the dimethylformamide, the residue is chromatographed on silica gel to yield the title product.

In Examples 206 to 209 the procedure is as in Example 205, starting from appropriate reactants.

**EXAMPLE 206 : 3-[2-(Acetylamino)ethyl]-2-phenyl-*1H*-pyrrolo[*2,3-b*]pyridin-5-yl (cyclohexylamino)methanethioate**

*Starting compound : Example 23*

**EXAMPLE 207 : 1-{2-[(Cyclopropylcarbonyl)amino]ethyl}-2,3-dihydro-*1H*-4-phenalenyl (propylamino)methanethioate**

*Starting compound : Example 33*

**EXAMPLE 208 : 3-{[(Cyclobutylcarbonyl)amino]methyl}-2-(3-phenyl-2-propenyl)benzo-[*b*]thiophen-5-yl anilinomethanethioate**

*Starting compound : Example 35*

**EXAMPLE 209 : 8-[(Butanoylamino)methyl]-6-(2-thienyl)-2-naphthyl (benzylamino)-methanethioate**

*Starting compound : Example 36*

**EXAMPLE 210 : Ethyl 9-[4-(cyclohexylamino)-4-oxobutyl]-1-methylnaphtho-[*2,1-b*]thiophene-2-carboxylate**

*Step A :* Ethyl 2-{[8-[4-(cyclohexylamino)-4-oxobutyl]-2-naphthyl]sulphanyl}-3-oxo-butanoate

Sodium (34 mmol) is added, with vigorous stirring, over a period of one hour, to a boiling solution of the product obtained in Example 13 (34 mmol) in 70 ml of anhydrous xylene. Stirring is continued, under reflux, for 2 hours and the mixture is allowed to cool to approximately 80°C. Ethyl chloro-2-acetylacetate (38 mmol) is then added dropwise. The mixture is then heated at reflux again for one hour. After cooling, the organic phase is washed with water, dried and concentrated to dryness under reduced pressure to yield the title product.

*Step B :* Ethyl 9-[4-(cyclohexylamino)-4-oxobutyl]-1-methylnaphtho[*2,1-b*]thiophene-2-carboxylate

The product obtained in Step A (18 mmol) is added all at once to 5 ml of sulphuric acid (d=1.81). The temperature of the reaction mixture rises rapidly to approximately 80°C. After stirring for 5 minutes, the mixture is poured into 100 ml of ice-cold water and is then extracted with dichloromethane. The organic phase is then washed with water, then with saturated sodium hydrogen carbonate solution and then again with water. The organic phase is then dried over magnesium sulphate and is then concentrated under reduced pressure. The residue is chromatographed to yield the title product.

In Examples 211 to 215 the procedure is as in Example 210, starting from appropriate reactants.

**EXAMPLE 211 : Ethyl 9-{2-[({[di(4-chlorophenyl)methyl]amino}carbonyl)amino]ethyl}-1-ethylnaphtho[*2,1-b*]thiophene-2-carboxylate**

*Starting compound : Example 15*

**EXAMPLE 212 : Ethyl 10-{3-[(cyclohexylcarbonyl)amino]propyl}-1-methyl-*3H*-benzo[*f*]-thiochromene-3-carboxylate**

*Starting compound : Example 16*

**EXAMPLE 213 : Isopropyl 9-[(acetylamino)methyl]-1-methyl-8,9-dihydro-*7H*-thieno-[3,2-f]chromene-2-carboxylate**

*Starting compound : Example 25*

**EXAMPLE 214 : Ethyl 10-[2-(acetylamino)ethyl]-1-methyl-3,8,9,10-tetrahydrothiopyrano-[3,2-f]thiochromene-3-carboxylate**

*Starting compound : Example 27*

**EXAMPLE 215 : Methyl 8-{[(cyclobutylcarbonyl)amino]methyl}-1-isopropyl-7-(3-phenyl-2-propenyl)thieno[*3',2' : 3,4*]benzo[*b*]thiophene-2-carboxylate**

*Starting compound : Example 35*

**EXAMPLE 216 : Ethyl 9-{2-[({[di-(4-chlorophenyl)methyl]amino}carbonyl)amino]ethyl}-1-ethyl-3-oxo-*3H*-3$\lambda^4$-naphtho[*2,1-b*]thiophene-2-carboxylate**

The procedure is as in Example 171, starting from Example 211.

**EXAMPLE 217 : Ethyl 10-{3-[(cyclohexylcarbonyl)amino]propyl}-1-methyl-4,4-dioxo-3,4-dihydro-4$\lambda^6$-benzo[*f*]thiochromene-3-carboxylate**

The procedure is as in Example 185, starting from Example 212.

**EXAMPLE 218 : N-[2-(1-Oxo-2,3-dihydro-*1H*-benzo[*f*]thiochromen-10-yl)ethyl]-3-(trifluoromethyl)benzamide**

*Step A :* Ethyl 3-{[8-(2-{[3-(trifluoromethyl)benzoyl]amino}ethyl)-2-naphthyl]sulphanyl}-propanoate

The procedure is as in Example 8, but the ethanethiol is replaced by ethyl 3-mercaptopropanoate and the product of Preparation 6 is used.

*Step B :* 3-{[8-(2-{[3-(Trifluoromethyl)benzoyl]amino}ethyl)-2-naphthyl]sulphonyl}-propanoic acid

A 0.5N aqueous solution of $K_2CO_3$ (10 ml) is added to the product obtained in Step A (4 mmol) dissolved in methanol (10 ml).
When the reaction has ceased, the solution is acidified to pH 6 using 1N HCl solution. The reaction mixture is extracted with dichloromethane. The organic phase is washed with water, dried over magnesium sulphate, concentrated under reduced pressure and chromatographed on silica gel to yield the title product.

*Step C :* 3-{[8-(2-{[3-(Trifluoromethyl)benzoyl]amino}ethyl)-2-naphthyl]sulphonyl-propanoyl chloride

The product obtained in Step B (3 mmol), dissolved in thionyl chloride, is stirred at 60°C under a current of nitrogen for one hour. The thionyl chloride is evaporated off under reduced pressure and the residue is dried with the aid of a vane pump to yield the title product.

*Step D :* N-[2-(1-Oxo-2,3-dihydro-*1H*-benzo[*f*]thiochromen-10-yl)ethyl]-3-(trifluoro-methyl)benzamide

The product obtained in Step C (3 mmol), dissolved in 1,1,2,2-tetrachloroethane (30 ml), is poured dropwise into a solution of aluminium chloride (10 mmol) in the same solvent (20 ml)

under nitrogen. The reaction mixture is heated at 60°C, with stirring, until the reaction has ceased. The solution is then poured into a mixture of ice (10 g) and concentrated HCl (0.3 ml) and stirring is carried out for one hour. The aqueous phase is extracted with chloroform (twice); the combined organic phases are then dried over magnesium sulphate, concentrated under reduced pressure and then chromatographed on silica gel to yield the title product.

In Examples 219 to 228, the procedure is as in Example 218, but the appropriate thiol and Preparation are used to obtain the title compound.

**EXAMPLE 219 : N-Cyclopropylmethyl-2-(1-oxo-2,3-dihydro-*1H*-benzo[*f*]thiochromen-10-yl)acetamide**

*Starting compound : Preparation 20*

**EXAMPLE 220 : N-[2-(2,2-Dimethyl-1-oxo-1,2-dihydronaphtho[*2,1-b*]thiophen-9-yl)ethyl]-N-methyl-N'-propylurea**

*Starting compound : Preparation 25*

**EXAMPLE 221 : N-[3-(1-Oxo-2,3,7,8,9,10-hexahydro-*1H*-benzo[*f*]thiochromen-10-yl)-propyl]acetamide**

*Starting compound : Preparation 100*

**EXAMPLE 222 : N-[2-(8-Benzyl-1-oxo-1,2-dihydro-*1H*-benzo[*f*]thiochromen-10-yl)ethyl]-1-cyclohexanecarboxamide**

*Starting compound : Preparation 48*

**EXAMPLE 223 : N-Methyl-4-(7,7-dimethyl-8-oxo-7,8-dihydrothieno[*3',2':3,4*]benzo[*f*]-furan-1-yl)butanamide**

*Starting compound : Preparation 54*

**EXAMPLE 224 : N-[(2-Benzyl-9-oxo-8,9-dihydro-*7H*-thieno[*3,2-f*]thiochromen-1-yl)-methyl]acetamide**

*Starting compound : Preparation 59*

**EXAMPLE 225 : N-[2-(7,7-Dimethyl-9-oxo-3,7,8,9-tetrahydrothiopyrano[*3,2-e*]indol-1-yl)-ethyl]benzamide**

*Starting compound : Preparation 66*

**EXAMPLE 226 : N-[(1-Oxo-1,7,8,9-tetrahydro-*2H*-thieno[*3,2-f*]chromen-9-yl)methyl]-acetamide**

*Starting compound : Preparation 82*

**EXAMPLE 227 : N-{[1-Oxo-8-(3-phenyl-2-propenyl)-2,3-dihydro-*1H*-benzo[*f*]-thiochromen-10-yl]methyl}-2-cyclohexylacetamide**

*Starting compound : Preparation 124*

**EXAMPLE 228 : N-[(3-Benzyl-9-oxo-8,9-dihydrothieno[*2',3':5,6*]benzo[*b*][*1,4*]dioxin-2-yl)-methyl]acetamide**

*Starting compound : Preparation 94*

**EXAMPLE 229 : N-[2-(2,3-Dihydro-*1H*-benzo[*f*]thiochromen-9-yl)ethyl]-3-(trifluoromethyl)benzamide**

The compound of Example 218 (3 mmol) is dissolved in acetic acid (70 ml) and, after several purges with argon, 10 % palladium-on-carbon (600 mg) is added and the mixture is placed under a hydrogen atmosphere. Stirring is carried out at ambient temperature until the reaction is complete and the palladium is filtered off over Celite. The acetic acid is evaporated off to dryness and the residue is chromatographed on silica gel to yield the title product.

In Examples 230 to 235, the procedure is as for Example 229, but the product of Example 218 is replaced by the appropriate reactant.

**EXAMPLE 230 : N-Cyclopropylmethyl-2-(2,3-dihydro-*1H*-benzo[*f*]thiochromen-10-yl)-acetamide**

*Starting compound : Example 219*

**EXAMPLE 231 : N-[2-(2,2-Dimethyl-1,2-dihydronaphtho[*2,1-b*]thiophen-9-yl)ethyl]-N-methyl-N'-propylurea**

*Starting compound : Example 220*

**EXAMPLE 232 : N-[(2-Benzyl-8,9-dihydro-*7H*-thieno[*3,2-f*]thiochromen-1-yl)methyl]-acetamide**

*Starting compound : Example 224*

**EXAMPLE 233 : N-[2-(7,7-Dimethyl-3,7,8,9-tetrahydrothiopyrano[*3,2-e*]indol-1-yl)ethyl]-benzamide**

*Starting compound : Example 225*

**EXAMPLE 234 : N-(1,7,8,9-Tetrahydro-*2H*-thieno[*3,2-f*]chromen-9-yl-methyl]acetamide**

*Starting compound : Example 226*

**EXAMPLE 235 : N-[(3-Benzyl-8,9-dihydrothieno[*2',3':5,6*]benzo[*b*][*1,4*]dioxin-2-yl)-methyl]acetamide**

*Starting compound : Example 228*

In Examples 236 to 239 the procedure is as in Example 171, starting from appropriate reactants.

**EXAMPLE 236 : N-[2-(1,4-Dioxo-1,2,3,4-tetrahydro-4$\lambda^4$-benzo[*f*]thiochromen-10-yl)-ethyl]-3-(trifluoromethyl)benzamide**

*Starting compound : Example 218*

**EXAMPLE 237 : N-Cyclopropylmethyl-2-(4-oxo-1,2,3,4-tetrahydro-4$\lambda^4$-benzo[*f*]-thiochromen-10-yl)acetamide**

*Starting compound : Example 230*

**EXAMPLE 238 : N-[2-(2,2-Dimethyl-3-oxo-2,3-dihydro-*1H*-3λ$^4$-naphtho[*2,1-b*]thiophen-9-yl)ethyl]-N-methyl-N'-propylurea**

*Starting compound : Example 231*

**EXAMPLE 239 : N-[2-(7,7-Dimethyl-6-oxo-6,7,8,9-tetrahydro-*3H*-6λ$^4$-thiopyrano[*3,2-e*]-indol-1-yl)ethyl]benzamide**

*Starting compound : Example 233*

In Examples 240 to 243 the procedure is as in Example 185, starting from appropriate substrates.

**EXAMPLE 240 : N-Methyl-4-(7,7-dimethyl-6,6,8-trioxo-7,8-dihydro-*6H*-6λ$^6$-thieno-[*3',2':3,4*]benzo[*f*]furan-1-yl)butanamide**

*Starting compound : Example 223*

**EXAMPLE 241 : N-Cyclopropylmethyl-2-(4,4-dioxo-1,2,3,4-tetrahydro-4λ$^6$-benzo[*f*]-thiochromen-10-yl)acetamide**

*Starting compound : Example 230*

**EXAMPLE 242 : N-[(3,3-Dioxo-1,2,3,7,8,9-hexahydro-3λ$^6$-thieno[*3,2-f*]chromen-9-yl)-methyl]acetamide**

*Starting compound : Example 234*

**EXAMPLE 243 : N-[(3-Benzyl-7,7-dioxo-8,9-dihydro-*7H*-7λ$^6$-thieno[*2',3':5,6*]benzo[*b*]-[1,4]dioxin-2-yl)methyl]acetamide**

*Starting compound : Example 235*

**EXAMPLE 244 : N-[2-(*3H*-Benzo[*f*]thiochromen-10-yl)ethyl]-2-bromoacetamide**

The product of Example 40 (10 mmol) and triethylene glycol are introduced into a two-necked flask. Heating is carried out at 160-170°C, under nitrogen and with stirring, for five hours. The reaction mixture is poured into ice-cold water and is extracted with ethyl acetate. The organic phase is washed with water and dried over calcium chloride. After filtration, the organic phase is

concentrated under reduced pressure. The residue is chromatographed on silica gel to yield the title product.

In Examples 245 to 260, the same method as in Example 244 is applied, but the product of Example 40 is replaced by the appropriate substrate.

**EXAMPLE 245 : N-Cyclobutyl-3-(*3H*-benzo[*f*]thiochromen-10-yl)propanamide**

*Starting compound : Example 52*

**EXAMPLE 246 : N-[2-(*3H*-Benzo[*f*]thiochromen-10-yl)ethyl]-N'-cyclobutylurea**

*Starting compound : Example 57*

**EXAMPLE 247 : Methyl 2-(*3H*-benzo[*f*]thiochromen-10-yl)-3-[(cyclopropylcarbonyl)-amino]propanoate**

*Starting compound : Example 64*

**EXAMPLE 248 : O-[(*3H*-Benzo[*f*]thiochromen-10-yl)methyl]-N-acetylhydroxylamine**

*Starting compound : Example 67*

**EXAMPLE 249 : N-[2-(3-Isopropyl-*3H*-benzo[*f*]thiochromen-10-yl)ethyl]acetamide**

*Starting compound : Example 73*

**EXAMPLE 250 : N-[2-(8-Benzoyl-*3H*-benzo[*f*]thiochromen-10-yl)ethyl]-N'-propylurea**

*Starting compound : Example 81*

**EXAMPLE 251 : N-[3-(7-Methyl-*7H*-thiochromeno[*6,5-b*]furan-1-yl)propyl]acetamide**

*Starting compound : Example 91*

**EXAMPLE 252 : O-{[(7-*tert*-Butyl-*7H*-thiochromeno[*6,5-b*]thiophen-1-yl)methyl]-N-thiopropionyl-hydroxylamine**

*Starting compound : Example 96*

**EXAMPLE 253 : N-Methyl-4-(3,7-dihydrothiopyrano[*3,2-e*]indol-1-yl)butanamide**

*Starting compound : Example 102*

**EXAMPLE 254 : N-{2-[2-(2-Methoxyphenyl)-3-methyl-3,7-dihydropyrrolo[*2,3-b*]-thiopyrano[*3,2-d*]pyridin-1-yl]ethyl}]acetamide**

*Starting compound : Example 107*

**EXAMPLE 255 : N-[2-(7-Cyclohexyl-2-phenyl-3,7-dihydropyrrolo[*2,3-b*]thiopyrano-[*3,2-d*]pyridin-1-yl]ethyl}]acetamide**

*Starting compound : Example 112*

**EXAMPLE 256 : N-[2-(2-Benzyl-7,8-dihydrothiepino[*3',2':3,4*]benzo[*b*]furan-1-yl)ethyl]-1-cyclopropanecarboxamide**

*Starting compound : Example 119*

**EXAMPLE 257 : N-[2-(1,2,3,8-Tetrahydrothiopyrano[*3,2-f*]chromen-1-yl)ethyl]acetamide**

*Starting compound : Example 127*

**EXAMPLE 258 : N-Methyl-3-(8-isopropyl-3,8-dihydrothiopyrano[*3,2-f*]chromen-1-yl)-propanamide**

*Starting compound : Example 131*

**EXAMPLE 259 : N-[2-(2,3-Dihydro-*8H*-thiochromeno[*5,6-b*][1,4]dioxin-2-yl)ethyl]-acetamide**

*Starting compound : Example 139*

**EXAMPLE 260 : N-{[2-(2-Furylmethyl)-*7H*-thiochromeno[*6,5-b*]furan-1-yl]methyl}-acetamide**

*Starting compound : Example 164*

**EXAMPLE 261 : N-Cyclobutyl-3-(2,3-dihydro-*1H*-benzo[*f*]thiochromen-10-yl)-propanamide**

Dissolve the product obtained in Example 245 (2 mmol) in 80 ml of methanol and cool with the aid of a bath of ice and salt. Add magnesium (80 mmol) in small portions and stir for 16 hours at ambient temperature. Add 30 $cm^3$ of 6N hydrochloric acid solution dropwise, while continuing to stir. Leave to cool, extract with ether, wash the organic phase with water, dry over magnesium sulphate, filter and concentrate under reduced pressure. The residue is chromatographed on silica gel to yield the title product.

In Examples 262 to 267 the procedure is the same as in Example 261, using appropriate reactants.

**EXAMPLE 262 : Methyl 3-[(cyclopropylcarbonyl)amino]-2-(2,3-dihydro-*1H*-benzo[*f*]-thiochromen-10-yl)propanoate**

*Starting compound : Example 247*

**EXAMPLE 263 : N-[3-(7,7-Dimethyl-8,9-dihydro-*7H*-thiochromeno[*6,5-b*]furan-1-yl)-propyl]acetamide**

*Starting compound : Example 251*

**EXAMPLE 264 : O-{[(7-*tert*-Butyl)-8,9-dihydro-*7H*-thieno[*3,2-f*]thiochromen-1-yl]-methyl}-N-thiopropionylhydroxylamine**

*Starting compound : Example 252*

**EXAMPLE 265 : N-{2-[2-(2-Methoxyphenyl)-3-methyl-3,7,8,9-tetrahydropyrrolo[*3,2-d*]-pyridin-1-yl]ethyl}acetamide**

*Starting compound : Example 254*

**EXAMPLE 266 : N-[2-(2-Benzyl-7,8,9,10-tetrahydrothiepino[*3',2':3,4*]benzo[*b*]furan-1-yl)-ethyl]-1-cyclopropanecarboxamide**

*Starting compound : Example 256*

**EXAMPLE 267 : N-[2-(2,3,9,10-Tetrahydro-*8H*-thiochromeno[*5,6-b*][*1,4*]dioxin-2-yl)-ethyl]acetamide**

*Starting compound : Example 259*

**EXAMPLE 268 : N-[2-(7-Amino-1-naphthyl)ethyl]-2-phenylacetamide**

*Step A :* N-[2-(7-Vinyl-1-naphthyl)ethyl]-2-phenylacetamide

15 mmol of the product obtained in Preparation 160, 16 mmol of vinyltributyltin and 0.43 mmol of tetrakis(triphenylphosphine)palladium are heated in 30 ml of N-methylpyrrolidinone at 110°C for 3 hours, with stirring. After evaporating off the solvent, the residue is taken up in 20 ml of dichloromethane and treated with 10 % aqueous potassium fluoride solution. After extraction, concentration under reduced pressure and chromatography on silica gel, the pure title product is obtained.

*Step B :* N-[2-(7-Formyl-1-naphthyl)ethyl]-2-phenylacetamide

To a solution of 10 mmol of the product obtained in Step A in a mixture of 50 ml of dioxane and 25 ml of water there are added, at ambient temperature, 1.10 g of osmium tetroxide in 2-methyl-2-propanol and then 8.70 g of sodium periodate. After stirring overnight at ambient temperature, the suspension is filtered and the filtrate is concentrated under reduced pressure. The residue obtained is taken up in dichloromethane. The organic phase is washed with water, dried and evaporated. The residue is purified by chromatography on silica gel to yield the title product.

*Step C :* 8-{2-[(2-Phenylacetyl)amino]ethyl}-2-naphthoic acid

2.7 g of potassium permanganate in 50 ml of an acetone/water mixture (50/50) are added, at ambient temperature, to a solution of 6.88 mmol of the product obtained in Step B in 30 ml of acetone. The solution is stirred for 2 hours at ambient temperature and is then filtered. The filtrate is concentrated under reduced pressure and chromatographed on silica gel to yield the title product.

*Step D :* 8-{2-[(2-Phenylacetyl)amino]ethyl}-2-naphthalenecarbonyl chloride

5 mmol of the product obtained in Step C are dissolved in 40 ml of thionyl chloride. After stirring under an inert atmosphere for 1 hour, the thionyl chloride is evaporated off under reduced pressure to yield the title product.

*Step E :* N-[2-(7-Amino-1-naphthyl)ethyl]-2-phenylacetamide

A solution of the product obtained in Step D (20 mmol) in dichloromethane (30 ml) containing tetrabutylammonium bromide (20 mg) is cooled in an ice bath. After adding sodium azide (24 mmol) dissolved in 5 ml of water, the solution is stirred vigorously at 0°C for 2 hours. The organic phase is separated off, washed with water (2 x 5 ml) and dried over magnesium sulphate. After filtration, trifluoroacetic acid (30 mmol) is added and the solution is stirred under reflux for 60 hours. After cooling, the organic phase is washed with saturated sodium hydrogen carbonate solution (2 x 5 ml) and is concentrated under reduced pressure. The residue is then taken up in methanol (20 ml); water (80 ml) and then potassium carbonate (30 mmol) are added. After stirring at ambient temperature for 20 hours, the reaction mixture is concentrated under reduced pressure to a volume of about 60 ml and is then extracted 3 times with ether (3 x 50 ml). After drying over sodium sulphate, the organic phase is filtered and then evaporated under reduced pressure. The residue is chromatographed on silica gel to yield the title product.

In Examples 269 to 289 the procedure is as in Example 268, starting from the appropriate substrate.

**EXAMPLE 269 : N-[2-(7-Amino-1-naphthyl)ethyl]-2-bromoacetamide**

*Starting compound : Preparation 198*

**EXAMPLE 270 : N-[2-(7-Amino-8-hexyl-1-naphthyl)ethyl]-2-phenylacetamide**

*Starting compound : Preparation 199*

**EXAMPLE 271 : N-Cyclohexyl-4-(7-amino-1-naphthyl)butanamide**

*Starting compound : Preparation 200*

**EXAMPLE 272 : N-[3-(7-Amino-1-naphthyl)propyl]acetamide**

*Starting compound : Preparation 201*

**EXAMPLE 273 : N-[2-(2-Amino-1-naphthyl)-1-methylethyl]propanamide**

*Starting compound : Preparation 202*

**EXAMPLE 274 : N-[2-(7-Amino-3-benzoyl-1-naphthyl)ethyl]-N'-propylurea**

*Starting compound : Preparation 167*

**EXAMPLE 275 : N-{2-[7-Amino-3-(cyclopropylmethyl)-1-naphthyl]ethyl}acetamide**

*Starting compound : Preparation 203*

**EXAMPLE 276 : N-Methyl-4-(5-aminobenzo[*b*]furan-3-yl)butanamide**

*Starting compound : Preparation 204*

**EXAMPLE 277 : N-[2-(5-Aminothieno[*3,2-b*]pyridin-3-yl)ethyl]acetamide**

*Starting compound : Preparation 205*

**EXAMPLE 278 : N-[2-(5-Amino-*1H*-3-indolyl)ethyl]benzamide**

*Starting compound : Preparation 206*

**EXAMPLE 279 : N-{2-[5-Amino-2-(4-fluorobenzyl)-1-methyl-*1H*-pyrrolo[*2,3-b*]pyridin-3-yl]ethyl}acetamide**

*Starting compound : Preparation 172*

**EXAMPLE 280 : N-[2-(5-Amino-2-benzylbenzo[*b*]furan-3-yl)ethyl]-1-cyclopropanecarboxamide**

*Starting compound : Preparation 207*

**EXAMPLE 281 : N-[(6-Amino-3,4-dihydro-*2H*-3-chromenyl)methyl]acetamide**

*Starting compound : Preparation 174*

**EXAMPLE 282 : N-[(6-Amino-2-phenyl-*2H*-3-chromenyl)methyl]butanamide**

*Starting compound : Preparation 208*

**EXAMPLE 283 : N-[2-(6-Amino-2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]acetamide**

*Starting compound : Preparation 179*

**EXAMPLE 284 : N-[(9-Amino-2,3-dihydro-*1H*-benzo[*f*]chromen-2-yl)methyl]-2-cyclopropylacetamide**

*Starting compound : Preparation 180*

**EXAMPLE 285 : N-(4-Amino-2,3-dihydro-*1H*-2-phenalenyl)-N'-cyclopropylthiourea**

*Starting compound : Preparation 181*

**EXAMPLE 286 : N-[2-(7-Amino-3-phenyl-1-naphthyl)ethyl]acetamide**

*Starting compound : Preparation 243*

**EXAMPLE 287 : N-(6-Amino-1,3,4,5-tetrahydrobenzo[*cd*]indol-4-yl)acetamide**

*Starting compound : Preparation 182*

**EXAMPLE 288 : N-Cyclobutyl-6-amino-4,5-dihydro-*3H*-benzo[*cd*]isobenzofuran-4-carboxamide**

*Starting compound : Preparation 183*

**EXAMPLE 289 : N-[2-(7-Amino-3-naphthyl-1-naphthyl)ethyl]heptanamide**

*Starting compound : Preparation 184*

**EXAMPLE 290 : N-{2-[7-(Diethylamino)-1-naphthyl]ethyl}-2-phenylacetamide**

To a solution of the product of Preparation 160 (5 mmol), diethylamine (12 mmol) and sodium tert-butoxide (14 mmol) in dioxane (20 ml) there are added tris(dibenzylideneacetone)-dipalladium (0.25 mmol, 1 mole percent of palladium) and tri(o-tolyl)phosphine (0.1 mmol).

Heating is then carried out at 100°C, with stirring, until all the starting compound has been used up (monitored by HPLC). The solution is then cooled to ambient temperature and 150 ml of ether are added. The organic phase is washed with brine (75 ml) and is then dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue is then chromatographed on silica gel to yield the title product.

In Examples 291 to 315 the procedure is as in Example 290, starting from the appropriate Preparation.

**EXAMPLE 291 : N-[2-(8-Allyl-7-piperidino-1-naphthyl)ethyl]-N'-cyclobutylthiourea**

*Starting compound : Preparation 161*

**EXAMPLE 292 : N-Cyclopropylmethyl-2-[7-(3,5-dimethylpiperazino)-1-naphthyl]-acetamide**

*Starting compound : Preparation 162*

**EXAMPLE 293 : N-Methyl-N-{2-[7-(methylanilino)-1-naphthyl]ethyl}-N'-propylurea**

*Starting compound : Preparation 163*

**EXAMPLE 294 : Methyl 2-[7-(*1H*-1-imidazolyl)-1-naphthyl]-3-[(2,2,2-trifluoroacetyl)-amino]propanoate**

*Starting compound : Preparation 164*

**EXAMPLE 295 : N-{3-[7-(Benzyl[1-ethynyl]amino)-1-naphthyl]propyl}-1-cyclohexane-carboxamide**

*Starting compound : Preparation 165*

**EXAMPLE 296 : N-{2-[7-(Hexylamino)-1,2,3,4-tetrahydro-1-naphthyl]ethyl}acetamide**

*Starting compound : Preparation 244*

**EXAMPLE 297 : N-{2-[3-Benzoyl-7-(propylamino)-1-naphthyl]ethyl}-N'-propylurea**

*Starting compound : Preparation 167*

**EXAMPLE 298** : **N-{3-[5-(Hexyl[2-propynyl]amino)benzo[*b*]furan-3-yl]propyl}acetamide**

*Starting compound : Preparation 168*

**EXAMPLE 299** : **N-{[2-Benzyl-5-([1-ethyl-2-propynyl]amino)benzo[*b*]thiophen-3-yl]-methyl}acetamide**

*Starting compound : Preparation 169*

**EXAMPLE 300** : **N-{2-[4-Allyl-5-(1-naphthylamino)benzo[*b*]thiophen-3-yl]ethyl}-benzamide**

*Starting compound : Preparation 170*

**EXAMPLE 301** : **N-[2-(5-Phenylamino-*1H*-3-indolyl)ethyl]-2-morpholinoacetamide**

*Starting compound : Preparation 171*

**EXAMPLE 302** : **N-{2-[2-(4-Fluorobenzyl)-5-(1-propenylamino)-1-methyl-*1H*-pyrrolo-[*2,3-b*]pyridin-3-yl]ethyl}acetamide**

*Starting compound : Preparation 172*

**EXAMPLE 303** : **N-{2-[6-(Methylanilino)-*1H*-benzo[*d*]imidazol-1-yl]ethyl}-1-cyclo-propanecarboxamide**

*Starting compound : Preparation 173*

**EXAMPLE 304** : **N-[(6-Piperidino-3,4-dihydro-*2H*-3-chromenyl)methyl]acetamide**

*Starting compound : Preparation 174*

**EXAMPLE 305** : **N-{2-[6-(Butyl[3-butynyl]amino)-3,4-dihydro-*2H*-4-chromenyl]ethyl}-2-phenylacetamide**

*Starting compound : Preparation 175*

**EXAMPLE 306** : **N-[(6-Morpholino-2-phenyl-*2H*-3-chromenyl)methyl]acetamide**

*Starting compound : Preparation 176*

**EXAMPLE 307 : N-[2-(6-Anilino-3,4-dihydro-*2H*-4-thiochromenyl)ethyl]acetamide**

*Starting compound : Preparation 177*

**EXAMPLE 308 : N-{2-[7-(Benzyl[methyl]amino)-1,4-benzodioxin-2-yl]ethyl}-N'-propylurea**

*Starting compound : Preparation 178*

**EXAMPLE 309 : N-{2-[6-(Diethylamino)-2,3-dihydro-1,4-benzodioxin-5-yl]ethyl}-N'-acetamide**

*Starting compound : Preparation 179*

**EXAMPLE 310 : N-{[9-(4,4-Dimethylpiperidino)-2,3,7,8,9,10-hexahydro-*1H*-benzo[*f*]-chromen-2-yl]methyl}-2-cyclopropylacetamide**

*Starting compound : Preparation 180*

**EXAMPLE 311 : N-[4-(Benzylamino)-2,3-dihydro-*1H*-2-phenalenyl]-N'-cyclopropyl-thiourea**

*Starting compound : Preparation 181*

**EXAMPLE 312 : N-[6-(Methylanilino)-1,3,4,5-tetrahydrobenzo[*cd*]indol-4-yl]acetamide**

*Starting compound : Preparation 182*

**EXAMPLE 313 : N-Cyclobutyl-6-(4-isopropylanilino)-4,5-dihydro-*3H*-benzo[*cd*]-isobenzofuran-4-carboxamide**

*Starting compound : Preparation 183*

**EXAMPLE 314 : N-{2-[7-(3,5-Dimethylpiperazino)-3-naphthyl-1-naphthyl]ethyl}-heptanamide**

*Starting compound : Preparation 184*

**EXAMPLE 315 : N-{2-[3-Phenyl-2-propenyl)-7-[(3-phenyl-2-propenyl]amino)-1-naphthyl]-ethyl}-2-cyclohexylacetamide**

*Starting compound : Preparation 185*

In Examples 316 to 322 the procedure is as in Example 244.

**EXAMPLE 316 : N-[2-(3-Benzyl-*3H*-benzo[*e*]indol-9-yl)propyl]-1-cyclohexane-carboxamide**

*Starting compound : Example 295*

**EXAMPLE 317 : N-[3-(6-Hexyl-6,7-dihydrofuro[*3,2-f*]quinolin-1-yl)propyl]acetamide**

*Starting compound : Example 298*

**EXAMPLE 318 : N-[(2-Benzyl-6-ethyl-6,7-dihydrothieno[3,2-f]quinolin-1-yl)methyl]-acetamide**

*Starting compound : Example 299*

**EXAMPLE 319 : N-[2-(7-Butyl-1,2,3,7,8,9-hexahydrochromeno[*6,5-b*]azepin-1-yl)ethyl]-2-phenylacetamide**

*Starting compound : Example 305*

**EXAMPLE 320 : N-Methyl-4-(7-oxo-7,8-dihydro-*6H*-furo[*3',2':3,4*]benzo[*b*]azepin-1-yl)-butanamide**

*Step A* : N-{3-[4-(Methylamino)-4-oxobutyl]benzo[*b*]furan-5-yl}-3-butynamide

A solution of butanoic acid chloride (10 mmol), dissolved in ether (5 ml), is added dropwise to a solution of the product obtained in Example 276 (10 mmol) in ether (10 ml) and triethylamine (2 ml). The solution is stirred at ambient temperature until the amine has disappeared (monitored by TLC). At the end of the reaction, the organic phase is washed with water, dried, concentrated under reduced pressure and chromatographed on silica gel to yield the title product.

*Step B* : N-Methyl-4-(7-oxo-7,8-dihydro-*6H*-furo[3',2':3,4]benzo[*b*]azepin-1-yl)-butanamide

The procedure is as in Example 244, starting from the compound obtained in Step A.

**EXAMPLE 321 : N-[2-(9-Benzyl-4-oxo-4,5-dihydro-*3H*-furo[*3',2':3,4*]benzo[*d*][1,3]-diazepin-10-yl)ethyl]-1-cyclopropanecarboxamide**

*Step A* : N-{2-[2-Benzyl-5-{[(1-ethynylamino)carbonyl]amino}benzo[*b*]furan-3-yl]ethyl}-1-cyclopropanecarboxamide

A solution of cyclohexyl isocyanate in dichloromethane (5 ml), is added dropwise to a solution of the product obtained in Example 280 (10 mmol) in dichloromethane (10 ml). Stirring is carried out at ambient temperature until the starting amine has disappeared (monitored by TLC); the reaction mixture is then evaporated and concentrated under reduced pressure and is then chromatographed on silica gel to yield the title product.

*Step B* : N-[2-(9-Benzyl-4-oxo-4,5-dihydro-*3H*-furo[3',2':3,4]benzo[*d*][1,3]diazepin-10-yl)ethyl]-1-cyclopropanecarboxamide

The procedure is as in Example 244, starting from the compound obtained in Step A.

**EXAMPLE 322 : N-Methyl-4-(4-thioxo-4,5-dihydro-*3H*-furo[*3',2':3,4*]benzo[*d*][1,3]-diazepin-10-yl)butanamide**

*Step A* : N-Methyl-4-{5-[([1-ethylamino]carbothioyl)amino]benzo[*b*]furan-3-yl}-butanamide

The procedure is as in Step A of Example 321, but the cyclohexyl isocyanate is replaced by 1-isothiocyanotoacetylene to obtain the title product.

*Step B* : N-Methyl-4-(4-thioxo-4,5-dihydro-*3H*-furo[*3',2':3,4*]benzo[*d*][1,3]diazepin-10-yl)butanamide

The procedure is as in Example 244, starting from the compound obtained in Step A.

In Examples 323 to 327 the procedure is as in Example 210, starting from appropriate substrates.

**EXAMPLE 323 : Ethyl 9-[2-phenylacetylamino)ethyl]-1-methyl-*3H*-benzo[*e*]indole-2-carboxylate**

*Starting compound : Example 268*

**EXAMPLE 324 : Ethyl 10-[4-(cyclohexylamino)-4-oxobutyl]-3,4-dihydrobenzo[*f*] quinoline-3-carboxylate**

*Starting compound : Example 271*

**EXAMPLE 325 : Ethyl 9-[2-(acetylamino)ethyl]-7-(cyclopropylmethyl)-*3H*-benzo[*e*] indole-2-carboxylate**

*Starting compound : Example 275*

**EXAMPLE 326 : Ethyl 2-[(butyrylamino)methyl]-3-phenyl-7,8-dihydro-*3H*-pyrano[*3,2-f*]-quinoline-8-carboxylate**

*Starting compound : Example 282*

**EXAMPLE 327 : Ethyl 10-[2-(heptanoylamino)ethyl]-1-isopropyl-8-naphthyl-3,4-dihydro-benzo[*f*]quinoline-3-carboxylate**

*Starting compound : Example 289*

**EXAMPLE 328 : N-[2-(1-Methyl-*3H*-benzo[*e*]indol-9-yl)ethyl]benzamide**

The compound obtained in Example 323 (5 mmol) is dissolved in ethanol (10 ml), to which 2N sodium hydroxide solution (6 ml) is added. The reaction mixture is heated at reflux until the reaction has ceased. Half the solvent is evaporated off. Extraction is carried out once with ether

and then the aqueous phase is acidified to pH = 1 with 1N potassium hydrogen sulphate solution. The aqueous phase is then extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulphate and concentrated under reduced pressure. The residue is chromatographed on silica gel to yield the title product.

In Examples 329 to 331 the procedure is as in Example 328, starting from appropriate substrates.

**EXAMPLE 329 : N-Cyclohexyl-4-(3,4-dihydrobenzo[*f*]quinolin-10-yl)butanamide**

*Starting compound : Example 324*

**EXAMPLE 330 : N-[(3-Phenyl-7,8-dihydro-*3H*-pyrano[*3,2-f*]quinolin-2-yl)methyl]-butanamide**

*Starting compound : Example 326*

**EXAMPLE 331 : N-[2-(1-Isopropyl-8-naphthyl-3,4-dihydrobenzo[*f*]quinolin-10-yl)ethyl]-heptanamide**

*Starting compound : Example 327*

**EXAMPLE 332 : N-[2-(4-Methyl-1-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinolin-10-yl)ethyl]-2-phenylacetamide**

*Step A* : Ethyl 3-{methyl-[8-(2-{[2-phenylacetyl]amino}ethyl)-2-naphthyl]amino}-propanoate

The procedure is as in Example 290, but the diethylamine is replaced by ethyl N-methyl-3-aminopropanoate.

*Step B* : 3-[Methyl(8-{2-[(2-phenylacetyl)amino]ethyl}-2-naphthyl)amino]propanoic acid

An aqueous 0.5N solution of $K_2CO_3$ (10 ml) is added to the product obtained in Step A (4 mmol) dissolved in methanol (10 ml). When the reaction has ceased, the solution is acidified to pH 6-7 using 1N hydrochloric acid solution. The reaction mixture is extracted with dichloromethane.

The organic phase is washed with water, dried over magnesium sulphate and concentrated under reduced pressure. The residue is chromatographed on silica gel to yield the title product.

*Step C :* 3-[Methyl-(8-{2-[(2-phenylacetyl)amino]ethyl}-2-naphthyl)amino]propanoyl chloride

The product obtained in Step B (3 mmol), dissolved in thionyl chloride, is stirred at 60°C under a stream of nitrogen for one hour. The thionyl chloride is evaporated off under reduced pressure and the residue is dried using a vane pump to yield the title product.

*Step D :* N-[2-(4-Methyl-1-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinolin-10-yl)ethyl]-2-phenylacetamide

The product obtained in Step C (3 mmol), dissolved in 1,1,2,2-tetrachloroethane (30 ml), is added dropwise to a solution of aluminium chloride (10 mmol) in the same solvent (20 ml) under nitrogen. The reaction mixture is heated at 60°C, with stirring, until the reaction has ceased and it is then poured into a mixture of ice (10 g) and concentrated HCl (0.3 ml); stirring is continued for one hour. The aqueous phase is extracted twice with chloroform; the combined organic phases are then dried over magnesium sulphate and concentrated under reduced pressure. The residue is chromatographed on silica gel to yield the title product.

In Examples 333 to 337 the procedure is as in Example 332, but starting from appropriate reactants.

**EXAMPLE 333 : N-[2-(7-Benzoyl-1-oxo-3-phenyl-2,3-dihydro-*1H*-benzo[*e*]indol-9-yl)-ethyl]-N'-propylurea**

*Starting compound : Preparation 167*

**EXAMPLE 334 : N-Methyl-4-(6-isopropyl-9-oxo-6,7,8,9-tetrahydrofuro[*3,2-f*]quinolin-1-yl)butanamide**

*Starting compound : Preparation 168*

**EXAMPLE 335 : N-{2-[2-(4-Fluorobenzyl)-3-methyl-9-oxo-6,7,8,9-tetrahydro-*3H*-pyrrolo-[*3,2-f*][*1,7*]naphthyridin-1-yl]ethyl}acetamide**

*Starting compound : Preparation 172*

**EXAMPLE 336 : N-[2-(8,8-Dimethyl-9-oxo-8,9-dihydro-*7H*-[*1,4*]dioxino[*2,3-e*]indol-2-yl)-ethyl]-N'-propylurea**

*Starting compound : Preparation 178*

**EXAMPLE 337 : N-(2-{4-Benzyl-1-oxo-8-[3-phenyl-2-propenyl]-1,2,3,4-tetrahydrobenzo-[f]quinolin-10-yl}ethyl)-2-cyclohexylacetamide**

*Starting compound : Preparation 185*

**EXAMPLE 338 : N-[2-(4-Methyl-1,2,3,4-tetrahydro[*f*]quinolin-10-yl)ethyl]-2-phenyl-acetamide**

The product of Example 332 (3 mmol) is dissolved in acetic acid (70 ml). After several purges with argon, 10 % palladium-on-carbon (600 mg) is added and the mixture is placed under a hydrogen atmosphere. Stirring is carried out at ambient temperature until the reaction is complete (monitored by TLC) and the palladium is filtered off over Celite. The acetic acid is evaporated off to dryness and the residue is chromatographed on silica gel to yield the title product.

In Examples 339 to 342 the procedure is as in Example 338, starting from appropriate reactants.

**EXAMPLE 339 : N-[2-(7-Benzoyl-3-phenyl-2,3-dihydro-*1H*-benzo[*e*]indol-9-yl)ethyl]-N'-propylurea**

*Starting compound : Example 333*

**EXAMPLE 340 : N-Methyl-4-(6-isopropyl-6,7,8,9-tetrahydrofuro[*3,2-f*]quinolin-1-yl)-butanamide**

*Starting compound : Example 334*

**EXAMPLE 341 : N-[2-(8,8-Dimethyl-8,9-dihydro-*7H*-[*1,4*]dioxino[*2,3-e*]indol-2-yl)ethyl]-N'-propylurea**

*Starting compound : Example 336*

**EXAMPLE 342 : N-[2-{4-Benzyl-8-[3-phenyl-2-propenyl]-1,2,3,4-tetrahydrobenzo[*f*]-quinolin-10-yl}ethyl)-2-cyclohexylacetamide**

*Starting compound : Example 337*

**EXAMPLE 343 : N-Cyclopropylmethyl-2-(1-hydroxy-2,3-dihydro-*1H*-benzo[*f*]-thiochromen-10-yl)acetamide**

A solution of the product obtained in Example 219 (2 mmol) dissolved in methanol (10 ml) is added dropwise to a suspension of sodium hydride (2.2 mmol) in methanol (50 ml) at -40°C. Stirring is carried out until the starting compound has completely disappeared (about 3 hours). At the end of the reaction, the solution is poured into water (30 ml). The reaction mixture is concentrated under reduced pressure to a volume of about 30 ml and is then extracted with ethyl acetate. The aqueous phase is washed with water, dried over magnesium sulphate and concentrated under reduced pressure. The residue is chromatographed on silica gel to yield the title product.

In Examples 344 to 349, the procedure is as in Example 343, but the product of Example 219 is replaced by the product of the appropriate Example.

**EXAMPLE 344 : N-Methyl-4-(8-hydroxy-7,7-dimethyl-7,8-dihydrothieno[*3',2':3,4*]benzo-[*f*]furan-1-yl)butanamide**

*Starting compound : Example 223*

**EXAMPLE 345 : N-[2-(9-Hydroxy-7,7-dimethyl-3,7,8,9-tetrahydro-thiopyrano[*3,2-e*]-indol-1-yl)ethyl]benzamide**

*Starting compound : Example 225*

**EXAMPLE 346 : N-[(3-Benzyl-9-hydroxy-8,9-dihydrothieno[*2',3':5,6*]benzo[*b*][*1,4*]dioxin-2-yl)methyl]acetamide**

*Starting compound : Example 228*

**EXAMPLE 347 : N-[2-(1-Hydroxy-4-methyl-1,2,3,4-tetrahydrobenzo[*f*]quinolin-10-yl)ethyl]-2-phenylacetamide**

*Starting compound : Example 332*

**EXAMPLE 348 : N-Methyl-4-(9-hydroxy-6-isopropyl-6,7,8,9-tetrahydrofuro[*3,2-f*]-quinolin-1-yl)butanamide**

*Starting compound : Example 334*

**EXAMPLE 349 : N-{2-[2-(4-Fluorobenzyl)-9-hydroxy-3-methyl-6,7,8,9-tetrahydro-*3H*-pyrrolo[*3,2-f*][*1,7*]naphthyridin-1-yl]ethyl}acetamide**

*Starting compound : Example 335*

Examples 350 to 353 are obtained by proceeding as in Example 268, starting from appropriate substrates.

**EXAMPLE 350 : N-[2-(5-Aminobenzo[b]furan-3-yl)ethyl]acetamide**

*Starting compound : Preparation 246*

**EXAMPLE 351 : N-[2-(7-Amino-1,2,3,4-tetrahydro-1-naphthyl)ethyl]acetamide**

*Starting compound : Preparation 244*

**EXAMPLE 352 : N-[2-(6-Amino-2,3-dihydro-*1H*-1-indenyl)ethyl]acetamide**

*Starting compound : Preparation 241*

**EXAMPLE 353 : N-{2-[5-(Methylamino)benzo[*b*]furan-3-yl)ethyl]acetamide**

The procedure is as in Example 290, starting from Preparation 246.

**EXAMPLE 354 : N-{2-[7-(Methylsulphinyl)-1-naphthyl]ethyl}acetamide**

1 eq. of the compound obtained in Example 1 is dissolved in anhydrous dichloromethane and is cooled with the aid of an ice bath. A solution of 1 eq. of *m*-chloroperbenzoic acid in dichloromethane is added dropwise and the mixture is stirred until the reaction is complete (monitored by TLC). The solvent is then evaporated off *in vacuo* and the residue obtained is taken up in saturated $Na_2CO_3$ solution. The precipitate formed, which corresponds to the title product, is filtered off.

**EXAMPLE 355 : N-{2-[7-(Methylsulphonyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 354 using 3 eq. of *m*-chloroperbenzoic acid.

**EXAMPLE 356 : N-{2-[7-(Methylthio)-1,2,3,4-tetrahydro-1-naphthyl]ethyl}acetamide**

*Step A* : 4-[4-(Methylthio)phenyl]-4-oxobutanoic acid

In a 500 ml flask with a ground neck, 0.17 mol of succinic anhydride is added to a solution of 0.17 mol of thioanisole in 140 ml of tetrachloroethane. The mixture is cooled with the aid of an ice bath, and 0.34 mol of aluminium chloride is added in small portions. The mixture is then heated at 60°C for 3 hours. The reaction mixture is then cooled, poured into ice-cold water and acidified with 3M HCl solution. The precipitate formed is filtered off under suction, washed with cyclohexane and recrystallised.

*Melting point = 153-155°C*

*Step B* : 4-[4-(Methylthio)phenyl]butanoic acid

In a 500 ml round-bottomed flask, 0.088 mol of the compound obtained in Step A is dissolved in 0.881 ml of trifluoroacetic acid. The solution is cooled to 0°C with the aid of an ice bath and 0.220 ml of triethylsilane hydride is added with the aid of a dropping funnel. The reaction mixture is stirred for 18 hours at ambient temperature and is then hydrolysed. The precipitate formed is filtered off under suction, is washed with water and with cyclohexane and is then

dissolved in ethyl acetate. The organic phase is dried over $MgSO_4$ and evaporated to obtain the title product in the form of a white solid.

*Melting point = 53-55°C*

*Step C :* 7-(Methylthio)-3,4-dihydro-1(*2H*)-naphthalenone

0.055 mol of the compound obtained in Step B and 100 g of polyphosphoric acid are introduced into a 500 ml round-bottomed flask. The reaction mixture is heated at 60°C for 3 hours and is then cooled and poured into water. Extraction with ethyl ether is carried out; the organic phase is washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue obtained is purified by chromatography on silica gel. Yellow oil

*Step D :* 2-[7-(Methylthio)-3,4-dihydro-1(*2H*)-naphthalenylidene]acetonitrile

0.041 ml of sodium hydride is suspended in 30 ml of anhydrous tetrahydrofuran under a nitrogen atmosphere in a 250 ml three-necked flask. Cooling is carried out in a bath of ice/salt and 0.041 ml of diethyl cyanomethylenephosphonate diluted with 40 ml of anhydrous tetrahydrofuran is added dropwise; magnetic stirring is carried out for 45 minutes. Whilst still cold, 0.031 mol of the compound obtained in Step C, dissolved in 30 ml of anhydrous tetrahydrofuran, is added dropwise. Stirring is carried out under a nitrogen atmosphere for 3 hours at ambient temperature. The reaction mixture is poured onto a mixture of water/ice, is acidified with aqueous 3M hydrochloric acid solution and is extracted 3 times with ethyl ether. The organic phase is dried over $MgSO_4$ and is evaporated. The residue obtained is recrystallised.

*Melting point = 59-61°C*

*Step E :* 2-[7-(Methylthio)-1,2,3,4-tetrahydro-1-naphthyl]-1-ethylamine hydrochloride

0.0046 mol of the compound obtained in Step D is dissolved in 70 ml of methanol. 0.0092 mol of cobalt chloride is added, with magnetic stirring, and then, in small portions, 0.0325 ml of sodium borohydride. Stirring is carried out for 3 hours at ambient temperature and the mixture is then acidified with 6M hydrochloric acid solution until the black precipitate dissolves. The methanol is evaporated off under reduced pressure and then extraction with ethyl ether is carried

out. The two phases are separated, and the aqueous phase is then rendered alkaline with 20 % ammonium hydroxide solution. Extraction with ethyl ether is carried out twice; the organic phase is dried over magnesium sulphate and evaporated under reduced pressure. The oil obtained is dissolved in alcohol at 95°C and then an ethanolic solution saturated with HCl is added. The solvent is evaporated off under reduced pressure and the residue obtained is recrystallised.

*Step F :* N-{2-[7-(Methylthio)-1,2,3,4-tetrahydro-1-naphthyl]ethyl}acetamide

In a 50 ml round-bottomed flask, 0.0025 mol of the compound obtained in Step E is dissolved in 5 ml of pyridine. The solution is cooled with the aid of an ice bath and 5 ml of acetic anhydride are added dropwise. Stirring is carried out for 5 hours at ambient temperature. The reaction mixture is poured into aqueous 3M hydrochloric acid solution and is then extracted with ethyl ether. The organic phase is washed with aqueous 10 % potassium carbonate solution and then with water, is dried over magnesium sulphate and is evaporated under reduced pressure. The residue obtained is recrystallised.

**EXAMPLE 357 : N-{2-[7-(Methylsulphinyl)-1,2,3,4-tetrahydro-1-naphthyl]ethyl}-acetamide**

The procedure is as in Example 354, starting from the compound obtained in Example 356.

**EXAMPLE 358 : N-{2-[7-(Methylsulphonyl)-1,2,3,4-tetrahydro-1-naphthyl]ethyl}-acetamide**

The procedure is as in Example 355, starting from the compound obtained in Example 356.

**EXAMPLE 359 : N-{2-[7-(Methylsulphinyl)-1-naphthyl]ethyl}butanamide**

The procedure is as in Example 354, starting from the compound obtained in Example 2.

**EXAMPLE 360 : N-{2-[7-(Methylsulphonyl)-1-naphthyl]ethyl}butanamide**

The procedure is as in Example 355, starting from the compound obtained in Example 2.

**EXAMPLE 361 : N-{2-[7-(Methylsulphinyl)-1-naphthyl]ethyl}cyclopropanecarboxamide**

The procedure is as in Example 354, starting from the compound obtained in Example 3.

**EXAMPLE 362 : N-{2-[7-(Methylsulphonyl)-1-naphthyl]ethyl}cyclopropanecarboxamide**

The procedure is as in Example 355, starting from the compound obtained in Example 3.

**EXAMPLE 363 : 2,2,2-Trifluoro-N-{2-[7-(methylsulphinyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 354, starting from the compound obtained in Example 4.

**EXAMPLE 364 : 2,2,2-Trifluoro-N-{2-[7-(methylsulphonyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 355, starting from the compound obtained in Example 4.

**EXAMPLE 365 : N-Methyl-N'-{2-[7-(methylsulphinyl)-1-naphthyl]ethyl}urea**

The procedure is as in Example 354, starting from the compound obtained in Example 5.

**EXAMPLE 366 : N-Methyl-N'-{2-[7-(methylsulphonyl)-1-naphthyl]ethyl}urea**

The procedure is as in Example 355, starting from the compound obtained in Example 5.

**EXAMPLE 367 : N-{2-[3-Benzoyl-7-(methylsulphinyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 354, starting from the compound obtained in Example 6.

**EXAMPLE 368 : N-{2-[3-Benzoyl-7-(methylsulphonyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 355, starting from the compound obtained in Example 6.

**EXAMPLE 369 : N-{2-[3-Benzyl-7-(methylsulphinyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 354, starting from the compound obtained in Example 7.

**EXAMPLE 370 : N-{2-[3-Benzyl-7-(methylsulphonyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 355, starting from the compound obtained in Example 7.

**EXAMPLE 371 : N-{2-[7-(Ethylsulphinyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 354, starting from the compound obtained in Example 8.

**EXAMPLE 372 : N-{2-[7-(Ethylsulphonyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 355, starting from the compound obtained in Example 8.

**EXAMPLE 373 : N-{2-[7-(Propylsulphinyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 354, starting from the compound obtained in Example 9.

**EXAMPLE 374 : N-{2-[7-(Propylsulphonyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 355, starting from the compound obtained in Example 9.

**EXAMPLE 375 : N-{2-[7-(Benzylthio)-1-naphthyl]ethyl}acetamide**

4.4 mmol of the compound obtained in Preparation 2 are dissolved in 20 ml of dichloromethane and the whole is introduced into a two-necked flask surmounted by a condenser and equipped

with a septum under a current of nitrogen. 6.5 mmol of benzylthiol are added by means of a syringe, and then 8.8 mmol of triflic acid. The mixture is heated at the reflux of dichloromethane for 24 hours. The mixture is cooled and then hydrolysed using 10 % $Na_2CO_3$ solution. The organic phase is washed with 10 % sodium hydroxide solution and then with water, until the washing waters are neutral, and is dried over $MgSO_4$, filtered and evaporated. The residue is taken up in ether and the precipitate formed is filtered off. The filtrate is evaporated, taken up in petroleum ether and the precipitate formed is filtered and then recrystallised from a mixture of toluene/cyclohexane (1/4).

*Melting point = 80-83°C*

**EXAMPLE 376 : N-{2-[7-(Benzylsulphinyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 354, starting from Example 375.

**EXAMPLE 377 : N-{2-[7-(Benzylsulphonyl)-1-naphthyl]ethyl}acetamide**

The procedure is as in Example 355, starting from Example 375.

# PHARMACOLOGICAL STUDY

**EXAMPLE A : Acute toxicity study**

Acute toxicity was evaluated after oral administration to groups each comprising 8 mice (26 ± 2 grams). The animals were observed at regular intervals during the course of the first day, and daily for the two weeks following treatment. The $LD_{50}$ (dose that causes the death of 50% of the animals) was evaluated and demonstrated the low toxicity of the compounds of the invention.

**EXAMPLE B : Melatonin receptor binding study on pars tuberalis cells of sheep**

Melatonin receptor binding studies of the compounds of the invention were carried out according to conventional techniques on pars tuberalis cells of sheep. The pars tuberalis of the adenohypophysis is in fact characterised in mammals by a high density of melatonin receptors (Journal of Neuroendocrinology, 1, pp. 1-4, 1989).

Protocol

1) Sheep pars tuberalis membranes are prepared and used as target tissue in saturation experiments to determine the binding capacities and affinities for 2-[$^{125}$I]-iodomelatonin.

2) Sheep pars tuberalis membranes are used as target tissue in competitive binding experiments using the various test compounds in comparison with melatonin.

Each experiment is carried out in triplicate and a range of different concentrations is tested for each compound. The results enable the determination, after statistical processing, of the binding affinities of the compound tested.

Results

The compounds of the invention appear to have a strong affinity for melatonin receptors.

**EXAMPLE C : Melatonin $mt_1$ and $MT_2$ receptor binding study**

The $mt_1$ or $MT_2$ receptor binding experiments are carried out using 2-[$^{125}$I]-melatonin as reference radioligand. The radioactivity retained is determined using a liquid scintillation counter.

Competitive binding experiments are then carried out in triplicate using the various test compounds. A range of different concentrations is tested for each compound. The results enable the binding affinities of the compounds tested ($IC_{50}$) to be determined.

The $IC_{50}$ values found for the compounds of the invention demonstrate binding to one or other of the $mt_1$ or $MT_2$ receptor sub-types, the values being $\leq 10\mu M$.

**EXAMPLE D : Action of the compounds of the invention on the circadian rhythms of locomotive activity of the rat**

The involvement of melatonin in influencing, by day/night alternation, the majority of physiological, biochemical and behavioural circadian rhythms has made it possible to establish a pharmacological model for research into melatoninergic ligands.

The effects of the molecules are tested on numerous parameters and, in particular, on the circadian rhythms of locomotive activity, which are a reliable indicator of the endogenous circadian clock.

In this study, the effects of such molecules on a particular experimental model, namely the rat placed in temporal isolation (permanent darkness), is evaluated.

Experimental protocol

One-month-old male rats are subjected, as soon as they arrive at the laboratory, to a light cycle of 12 hours' light per 24 hours (LD 12 : 12).

After 2 to 3 weeks' adaptation, they are placed in cages fitted with a wheel connected to a recording system, in order to detect the phases of locomotive activity and thus monitor the nychthemeral rhythms (LD) or circadian rhythms (DD).

As soon as the rhythms recorded show a stable pattern during the light cycle LD 12 : 12, the rats are placed in permanent darkness (DD).

Two to three weeks later, when the free course (rhythm reflecting that of the endogenous clock) is clearly established, the rats are given a daily administration of the molecule to be tested.

The observations are made by means of visualisation of the rhythms of activity :

- influence on the rhythms of activity by the light/dark cycle,
- disappearance of the influence on the rhythms in permanent darkness,
- influence on the activity by the daily administration of the molecule; transitory or durable effect.

A software package makes it possible :

- to measure the duration and intensity of the activity, the period of the rhythm of the animals during free course and during treatment,
- possibly to demonstrate by spectral analysis the existence of circadian and non-circadian (for example ultradian) components.

Results

The compounds of the invention clearly appear to allow powerful action on the circadian rhythm *via* the melatoninergic system.

**EXAMPLE E : Light/dark cages test**

The compounds of the invention are tested on a behavioural model, the light/dark cages test, which allows the anxiolytic activity of the compounds to be demonstrated.

The apparatus consists of two polyvinyl boxes covered with Plexiglass. One of the boxes is in darkness. A lamp is placed above the other box, yielding a light intensity of approximately 4000 lux in the centre of the box. An opaque plastic tunnel separates the light box from the dark box. The animals are tested individually for a session of 5 minutes. The floor of each box is cleaned between each session. At the start of each test, the mouse is placed in the tunnel, facing the dark box. The time spent by the mouse in the illuminated box and the number of passages through the tunnel are recorded after the first entry into the dark box.

After administration of the compounds 30 minutes before the start of the test, the compounds of the invention significantly increase the time spent in the illuminated cage and the number of passages through the tunnel, which demonstrates the anxiolytic activity of the compounds of the invention.

**EXAMPLE F : Activity of compounds of the invention on the caudal artery of the rat**

The compounds of the invention were tested *in vitro* on the caudal artery of the rat. Melatoninergic receptors are present in those vessels, thus providing a relevant pharmacological model for studying melatoninergic ligand activity. The stimulation of the receptors can cause either vasoconstriction or dilation depending on the arterial segment studied.

Protocol

One-month old rats are accustomed to a light/dark cycle of 12h/12h during a period of 2 to 3 weeks.

After sacrifice, the caudal artery is isolated and maintained in a highly oxygenated medium. The arteries are then cannulated at both ends, suspended vertically in an organ chamber in a suitable

medium and perfused *via* their proximal end. The pressure changes in the perfusion flow enable evaluation of the vasoconstrictive or vasodilatory effect of the compounds.

The activity of the compounds is evaluated on segments that have been pre-contracted by phenylephrine (1µM). A concentration/response curve is determined non-cumulatively by the addition of a concentration of the test compound to the pre-contracted segment. When the observed effect reaches equilibrium, the medium is changed and the preparation is left for 20 minutes before the addition of the same concentration of phenylephrine and a further concentration of the test compound.

Results

The compounds of the invention significantly modify the diameter of caudal arteries pre-constricted by phenylephrine.

**EXAMPLE G : Pharmaceutical composition : tablets**

1000 tablets each comprising 5 mg of N-{2-[7-methylthio)-1-naphthyl-ethyl}acetamide (Example 1) ..... 5 g
wheat starch ..... 20 g
maize starch ..... 20 g
lactose ..... 30 g
magnesium stearate ..... 2 g
silica ..... 1 g
hydroxypropyl cellulose ..... 2 g